Continuous Glucose Monitoring in Subjects After Simultaneous Pancreas-Kidney and Kidney-Alone Transplantation

Luisa M. Rodríguez, M.D.,¹ Richard J. Knight, M.D., F.A.C.S.,² and Rubina A. Heptulla, M.D.¹

Abstract

Background: Simultaneous pancreas-kidney (SPK) transplantation is an important replacement therapy for individuals with diabetes and end-stage renal disease. Kidney-alone (KA) transplantation is associated with a high incidence of post-transplant diabetes.

Methods: This was a cross-sectional study. We studied 48-h glucose concentrations in eight subjects with type 1 diabetes mellitus after SPK transplantation, six subjects post-KA transplantation, and nine healthy controls using the CGMS[®] (Medtronic Minimed, Northridge, CA) continuous glucose monitoring system.

Results: The 48-h mean glucose concentration was 101 ± 7 mg/dL in the SPK subjects, 105 ± 12 mg/dL in the KA subjects, and 99 ± 7 mg/dL in the healthy controls. The glycemic excursions were higher in the KA group compared to the SPK cohort and healthy controls ($P < 0.0001$). No differences in the incidence of hypoglycemia were detected among the three groups. Significant postprandial hyperglycemia was uncovered in four of the six KA subjects.

Conclusions: SPK transplantation is very effective at normalizing glycemic excursions. Unsuspected hyperglycemia was identified in the KA group. The CGMS was a useful ambulatory tool to study glucose profiles in the post-transplant period and may help uncover hyperglycemia undetected by routine laboratory testing.

Background

TYPE 1 DIABETES MELLITUS (T1DM) is a chronic disease characterized by deficient insulin secretion.¹ Whole-organ pancreas transplantation successfully restores endogenous insulin secretion in patients with T1DM.² During the last decade, advances in both surgical technique and immunosuppressive therapy have improved the outcomes of whole-organ pancreas transplantation.^{2–6} In the absence of organ rejection, the transplanted pancreas restores euglycemia, achieves insulin independence, and prevents further macrovascular complications related to T1DM.⁷ The simultaneous pancreas-kidney (SPK) transplantation is the preferred procedure for patients with T1DM and end-stage renal disease.

The Diabetes Control and Complication Trial demonstrated that hypoglycemia was a major limiting factor in the use of intensified insulin regimen in T1DM.⁸ Individuals with T1DM have abnormal glucagon and epinephrine counterregulatory responses.^{9–11} The ability to perceive hypoglycemia is also compromised, increasing the risk related to it.¹² Successful whole-pancreas transplantation improves glucagon and epinephrine responses to hypoglycemia. Although

significant improvements in counterregulatory responses have been shown in previous studies, the responses are not as robust as in the healthy state.^{13,14} The systemic venous drainage of the pancreas graft as opposed to portal delivery of insulin results in peripheral hyperinsulinemia, suggesting the risk for hypoglycemia may persist after whole-organ pancreas transplantation.

Kidney-alone (KA) transplantation is the most common transplant procedures performed in the United States. Post-transplant diabetes is a serious complication in KA transplantation associated with decreased graft survival.^{15,16} The incidence of post-transplant diabetes in KA transplantation has been reported up to 53%.¹⁷ Early identification of glucose intolerance in patients at high risk can be beneficial to prevent progression to diabetes.

The CGMS[®] (Medtronic Minimed, Northridge, CA) continuous glucose monitoring system uses a glucose oxidase-based sensor to measure interstitial glucose in subcutaneous tissue and is calibrated against corresponding fingerstick glucose values. The sensor is inserted subcutaneously in the office setting and allows us to measure glucose concentrations every 5 min for up to 72 h.¹⁸ The sensor is connected to a

¹Endocrinology Section, Department of Pediatrics, Baylor College of Medicine; and ²Division of Pancreas Transplantation, Department of Surgery, The Methodist Hospital, Houston, Texas.

pager-size portable monitor with recording capability. The information is downloaded to a data processing computer program and permits the study of glucose variability. The purpose of this study was to use the CGMS to study glycemic excursions in SPK, KA, and healthy controls. The primary goal of the study was to identify differences in glycemic excursions and frequency of hyper- and hypoglycemia among the three study groups.

Subjects and Methods

The study was approved by the Institutional Review Board of the two participating centers, and written informed consent was obtained in all subjects. The study population consisted of three groups: subjects with history of T1DM and SPK transplantation, subjects with history of KA transplantation, and healthy controls. The KA and healthy subjects had negative history of diabetes. The pancreas transplantation used systemic venous drainage and enteric exocrine drainage without a Roux-en Y limb. The kidney grafts were placed in an intraabdominal position. The KA transplantation was performed using a standard retroperitoneal approach via a curvilinear lower quadrant incision. All transplant recipients were on maintenance immunosuppression, which consisted of sirolimus (Rapamune®, Wyeth, Philadelphia, PA), cyclosporine (Neoral®, Novartis, East Hanover, NJ), and prednisone. The SPK and KA subjects had normal renal function tests at the time of the study.

The subjects were recruited at a routine post-transplant clinic visit. The study visit consisted of a 72-h monitoring period with the CGMS, which was inserted into the subcutaneous tissue of the anterior abdominal wall. The subjects returned the monitor after 72 h, and the glucose concentration data were downloaded to a computer program for analysis. Glucose monitor data for a continuous 48-h period were used for analysis. The subjects were instructed to maintain their usual daily activities, diet, and medications during the monitoring period. A glucometer was provided to perform self-monitoring of blood glucose. The subjects obtained four fingerstick blood glucose levels (before meals and at bedtime) daily and entered the values into the CGMS for calibration purposes. Subjects were oriented as to signs and symptoms of hypoglycemia and instructed to document the time and duration of symptoms and to check fingerstick blood glucose immediately. Episodes of unrecognized hypoglycemia were determined by comparing the CGMS data to the subject's self-blood glucose monitoring and log reports. Hypoglycemia was defined as a blood glucose concentration of <60 mg/dL, normoglycemia if blood glucose concentration was between 60 and 140 mg/dL, and hyperglycemia as a glucose level above 140 mg/dL. The number of hypoglycemic episodes (per subject day) was quantified. A hypoglycemic episode was defined as continuous monitor glucose levels less than 60 mg/dL for ≤ 10 min.

The main outcome variables included 48-h mean glucose concentrations, glycemic excursions, and quantification of hypoglycemic episodes as measured by CGMS. Analysis of the duration of time the subjects spent in the hypo-, normo-, and hyperglycemic ranges was determined for the total 48-h period of monitoring and was expressed as a percentage of the total time. Other variables included incremental area under the curve for glucose (AUC), calculated by the trapezoidal

rule. Analysis of variance for repeated measures was performed to compare the three groups. Statistical analysis was performed through GraphPad (San Diego, CA) Prism version 5. A value of $P \leq 0.05$ was considered significant.

Results

The demographics and characteristics of the study subjects are shown in Table 1. The SPK group consisted of eight subjects with a mean duration of T1DM of 24 ± 4 years. Testing occurred at a mean time of 1 year post-transplantation (range, 0.3–2 years). All SPK recipients were insulin free, with a normal mean post-transplant hemoglobin A_{1c} level of $5.4 \pm 3\%$. The KA group consisted of seven subjects post-kidney transplantation with no history of diabetes. Testing occurred at a mean time of 3 years post-transplantation (range, 1–9 years). The KA subjects were maintained on the same immunosuppressive regimen as the SPK group. The control group included 10 healthy individuals not taking medications. Two subjects were excluded from the analysis (one in the KA and one from the control group) because of insufficient CGMS data.

The glycemic profiles of the three study groups are illustrated in Figure 1. The KA subjects had higher 48-h glycemic excursions compared to the SPK and control groups ($P < 0.0001$). Episodes of extreme postprandial hyperglycemia with blood glucose concentration above 200 mg/dL were identified in four KA subjects. No postprandial hyperglycemia was identified in the SPK and control groups. The 48-h glycemic excursions were not different between the SPK and control groups. The 48-h mean glucose concentrations of the SPK, KA, and control subjects were 101, 105, and 99 mg/dL, respectively. Table 1 also shows the results of the AUC_(glucose 48h) analysis. No significant difference was detected in the AUC_(glucose 48h) among the three groups ($P = 0.09$). The duration of the glycemic excursions (hypoglycemic, normoglycemic, and hyperglycemic) in the 48-h period was quantified for the three study groups (Table 1). The time duration of hyperglycemia was increased by threefold in the KA group compared to SPK subjects; however, the difference was not statistically significant ($P = 0.06$). There were no differences among the groups in the percentage of time the subjects spent in the hypoglycemic and euglycemic ranges.

Discussion

This study was conducted to assess glycemic excursions in the post-transplant period using the CGMS. We studied continuous glucose monitoring data in SPK, KA, and healthy controls. Significant elevation in glycemic excursions was identified in the KA recipients. The SPK and healthy controls had comparable glycemic excursions. We did not find a significant difference in quantitative hypoglycemia among the groups. To our knowledge, this is the first study that has compared glycemic excursions of SPK, KA, and healthy subjects. A significant finding of our study was the identification of hyperglycemia in the KA recipients. Poorly controlled diabetes mellitus is the leading cause of end-stage renal disease in the United States.¹⁹ The identification of clinically significant postprandial hyperglycemia in KA recipients is of concern as the immunosuppressive agents routinely used—prednisone, tacrolimus, and cyclosporine—are associated with the development of post-transplant

TABLE 1. CLINICAL CHARACTERISTICS AND GLYCEMIC EXCURSIONS

	SPK	KA	C	P value
Number of patients	8	6	9	
Age (years)	39 ± 7	35 ± 12	39 ± 8	
Sex (M/F)	5/3	3/3	5/4	
BMI (kg/m ²)	27 ± 4	25 ± 4	26 ± 3	
Mean 48-h glucose (mg/dL)	101 ± 10	105 ± 10	99 ± 5	0.0001
AUC _(glucose 48h) (mg/dL · min)	102 ± 9	104 ± 14	99 ± 7	0.09
Hypoglycemic episodes (per subject/day)	0.06	0.03	0.01	0.19
Time in glycemic excursions (%)				
Hypoglycemia	2	1	0	0.23
Euglycemia	96	91	99	0.14
Hyperglycemia	2	8	1	0.06

Data are mean ± SD values. BMI, body mass index.

diabetes.¹⁶ Routine fasting plasma glucose concentration is insufficient to uncover postprandial hyperglycemia, which is an early finding in diabetes mellitus.²⁰ In a prospective study, the development of post-transplant diabetes in KA recipients was found to be a predictor of cardiac death and acute myocardial infarction.²¹ This report suggests that annual surveillance with a formal 2-h glucose challenge may be needed for assessment of early glucose intolerance or frank diabetes in this high-risk population. More prospective studies examining glucose tolerance of KA recipients in the post-transplant period are necessary.

Successful whole-organ pancreas transplantation restores glucose-stimulated insulin secretion.⁶ Despite a large body of literature examining the counterregulatory responses after whole-organ pancreas transplantation, the information is inconclusive. In 1994 Barrou et al.¹³ and in 1990 Diem et al.¹⁴ studied glucagon secretion in the post-transplant period using hyperinsulinemic hypoglycemic clamp studies. They reported improved glucagon secretion to hypoglycemia compared with non-transplanted individuals with T1DM. Both studies showed improvement in glucagon secretion but not normalization compared with normal individuals. However, reports

from Luzi et al.²² and Battezzati et al.²³ demonstrated that there was no improvement in glucagon secretion after pancreas transplantation. A study examining hypoglycemia counterregulatory response in long-term post-pancreas transplant individuals (in the range of 5–19 years post-transplantation) revealed adequate increase in plasma glucagon in response to hypoglycemia but suboptimal epinephrine response compared with normal individuals.²⁴ Redmon et al.²⁵ studied 24-h glucose concentrations in pancreas transplant recipients with history of hypoglycemic symptoms in the post-transplant period. They accomplished this by measuring hourly glucose concentrations. In this study transient postprandial hypoglycemia was identified in 40% of the subjects with history of hypoglycemic symptoms in the post-transplant period. However, hypoglycemia resolved spontaneously with no intervention. A limitation of this study was the infrequent glucose measurements. In this study the glucose concentration was assessed hourly, and the investigators may have missed short episodes of transient hypoglycemia. More frequent glucose measurements can be collected with the CGMS.

Using CGMS Kessler et al.²⁶ compared glycemic excursions of SPK transplantation recipients, islet after kidney transplantation

FIG. 1. Mean 24-h glucose excursions in SPK, KA, and control subjects. BG, blood glucose.

recipients, and T1DM intensively treated patients. They showed significant reduction in glucose variability without hypoglycemia in the SPK subjects. No healthy controls were included in this study. To our knowledge no study has compared real-time continuous glucose profiles of SPK, KA, and healthy subjects. We showed no significant difference in the occurrence of hypoglycemic episodes of SPK subjects compared to KA and healthy controls. Although the frequency of hypoglycemic episodes (per subject/day) was higher in the SPK group compared to the controls (0.06 vs. 0.01), the difference was not statistically significant. Our results are concordant with the previous report from Kessler et al.²⁶ This study adds to the cumulative experience in humans showing that clinically significant hypoglycemia is not of concern for patients with history of diabetes after SPK transplantation.

We acknowledge the limitations of our study. The number of participants in the KA group was small, and failure to find statistical significance for some of the end points can be a Type 2 error due to the small sample size. Poorly controlled diabetes mellitus is the leading cause of end-stage renal disease in the United States.¹⁹ It was very difficult to find KA subjects with no history of glucose intolerance or diabetes. A 2-h glucose tolerance test was not performed in the KA and control groups, to exclude subjects with impaired glucose tolerance. According to our findings a glucose tolerance test is an important test to consider in future studies to exclude subjects with impaired glucose tolerance or undiagnosed diabetes. The carbohydrate intake and physical activity of the study participants were not controlled. For this reason, we cannot exclude the possibility that our findings could be explained by variations in the subject's diet or physical activity.

In summary, we have compared glucose excursions in SPK, KA, and healthy controls using CGMS. We identified significant unrecognized hyperglycemia in KA subjects, and no difference in the incidence of hypoglycemia was detected among the three groups. This information should be used to increase awareness of abnormalities in glycemic excursions in patients after kidney transplantation. More studies are needed to investigate the impact of these abnormalities in the long-term glycemic control of these patients. The CGMS was found to be a useful ambulatory tool to study glucose profiles in subjects in the post-transplant period and may help uncover postprandial hyperglycemia missed with routine laboratory testing.

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Author Disclosure Statement

The authors have no competitive financial interests to disclose.

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- Address correspondence to:
Luisa M. Rodríguez, M.D.
Endocrinology Section
Department of Pediatrics
6621 Fannin, MC: CC 1020
Houston, TX 77030
E-mail: lrodrigu@bcm.tmc.edu