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CONTINUOUS GLUCOSE MONITORING SYSTEM FOR EARLY DETECTION OF GRAFT DYSFUNCTION IN ALLOGENIC ISLET TRANSPLANT RECIPIENTS

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Abstract

Background—There are no effective indicators of graft dysfunction in islet transplantation. This study evaluated the role of the Continuous Glucose Monitoring System (CGMS) as an early indicator of graft dysfunction in islet transplant recipients.

Methods—In 5 islet allograft recipients, we retrospectively determined the date of graft dysfunction: three fasting blood glucose levels >7.8mmol/L (140mg/dL) and/or three postprandial blood glucose levels >10mmol/L (180mg/dL) in one week. We then determined two time points in respect to graft dysfunction: 5 to 9 months before (time point A) and 2 to 3 months before (time point B). For these two time points we assessed: HbA1c, C-peptide (CP), C-peptide glucose ratio (CPGR), 90-minute glucose from mixed meal tolerance test, and percentage of capillary blood glucose levels above 7.8 mmol/L (%CBG>7.8) in a 15 day interval (one week before and after CGMS placement). From the CGMS recordings we calculated the glucose variability and the percentage of time spent in hyperglycemia >7.8 mmol/L (%HGT>7.8) and >10mmol/L (%HGT>10).

Results—No difference was found between time point A and B for the following parameters: HbA1c, CP, CPGR, 90 minute glucose, %CBG>7.8 and %HGT>10. We observed a statistically significant increase from time point A to B in glucose variability (1.1±0.5 mmol/L to 1.6±0.6 mmol/L, p=0.004), and in the %HGT >7.8 (11±12% to 22±18%, p=0.036).

Conclusion—Glucose variability and %HGT >7.8 determined by CGMS are useful as early indicators of graft dysfunction in islet transplant recipients. Further studies with larger sample size will help validate these observations.

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INTRODUCTION

Islet transplantation (IT) under steroid free immunosuppression has a role as a potential treatment for patients with type 1 diabetes with severe hypoglycemia and hypoglycemia unawareness [1] [2] [3]. Despite the achievement of a more physiological glycemic control than exogenous insulin administration, most patients sustain a decline of islet allograft function over time [3] [4] [5] [6]. Unfortunately, there are no effective indicators for the early detection of graft dysfunction in IT patients. The use of the Continuous Glucose Monitoring System (CGMS) represents an improvement in the metabolic evaluation of patients with type 1 diabetes treated with IT [7,8]. The CGMS has been used to evaluate the metabolic control of type 1 diabetes patients who achieved insulin independence, providing a display of the glycemic stability obtained with IT as compared to pre-transplant conditions [7] [9]. The objective of this study was to determine the role of CGMS as an early indicator of graft dysfunction.

METHODS

In 18 recipients of two consecutive islet allografts, who belonged to different islet transplant protocols and underwent treatment with steroid free immunosuppression, we retrospectively determined the date of graft dysfunction, defined as the occurrence of at least three fasting capillary blood glucose levels $>7.8\text{mmol/L}$ (140mg/dl) and/or three postprandial capillary blood glucose levels $>10\text{mmol/L}$ (180mg/dl) in one week. We then retrospectively assessed those patients who had at least two consecutive CGMS recordings before graft dysfunction. Due to the unpredictable occurrence of graft dysfunction, and the relatively recent implementation of the CGMS, only five patients had at least two consecutive CGMS recordings in the nine months prior to their graft dysfunction and were included in this analysis. The CGMS recordings were performed at two different time points: 5 to 9 months before (time point A) and 2 to 3 months before (time point B) graft dysfunction. For both time points A and B the following parameters were assessed: HbA1c (measured by high-pressure liquid chromatography), C-peptide (CP, measured by double antibody radioimmunoassay on fasting blood samples), C-peptide glucose ratio (CPGR: $[\text{C-peptide (ng/ml)}/\text{glucose (mg/dl)}] \times 100$), 90-minute glucose from mixed meal tolerance test [10], and the percentage of capillary blood glucose (monitored up to 7 times a day in early post transplant period and less frequently in the late post transplant period) levels above 7.8mmol/L ($\%CBG>7.8$) in a 15 day interval (one week before and ending one week after the placement of CGMS). For the CGMS recordings, the sensor was placed subcutaneously for 72 hours, and the following parameters were analyzed for both time points A and B: a) glucose variability calculated as the mean of the absolute value of measured glucose minus 5.5 mmol/L [8]; b) the percentage of time spent in hyperglycemia $>7.8\text{mmol/L}$ ($\%HGT>7.8$; total number of minutes above a glucose level of 7.8 mmol/L in the 72 hour period of CGMS recordings expressed as a percentage), and c) the percentage of time spent in hyperglycemia $>10\text{ mmol/L}$ ($\%HGT>10$; total number of minutes above a glucose level of 10 mmol/L in the 72 hour period of CGMS recordings expressed as a percentage). All statistical analyses were expressed as means $\pm$ standard deviations (SD) or in medians and ranges in the case of nonparametric variables. Group comparisons were analyzed by t-test for dependent samples. P values <0.05 were considered significant.

RESULTS

The 5 subjects analyzed had a median age of 44 years (range, 32 to 56) and a median duration of diabetes of 30 years (range, 19 to 35). There were 4 females and 1 male. Four patients achieved insulin independence after receiving 2 islet infusions and one patient after receiving 1 infusion. Study subjects received a total mean of $12,926 \pm 2,944\text{ IEQ/kg}$. Graft dysfunction occurred in a median time of 15 months (range of 8 to 39).

In Table 1 we show the results of the different parameters assessed at the different time points. For time point A we found: HbA1c, $5.8 \pm 0.3\%$; CP, 1.58 ± 0.41 ng/ml; CPGR, 1.58 ± 0.44 ; 90-minute glucose, 7.7 ± 1.1 mmol/L (138 ± 20 mg/dl); %CBG>7.8, $13.2 \pm 14.2\%$; glucose variability, 1.1 ± 0.5 mmol/L (20.2 ± 8.4 mg/dl); %HGT>7.8, $11 \pm 12\%$; %HGT>10, $1 \pm 1.7\%$. For time point B: HbA1c, $6 \pm 0.1\%$; CP, 1.8 ± 0.7 ng/ml; CPGR, 1.5 ± 0.5 ; 90-minute glucose, 8.3 ± 1.4 mmol/L (149 ± 24 mg/dl); %CBG>7.8, $9.8 \pm 8.9\%$; glucose variability, 1.6 ± 0.6 mmol/L (29.2 ± 10.4 mg/dl); %HGT>7.8, $22 \pm 18\%$; %HGT>10, $3 \pm 5.1\%$ for time point B. There was no difference between time point A and B for HbA1c, CP, CPGR, 90-minute glucose, %CBG>7.8, and %HGT>10. There was an increase between time points A and B for glucose variability ($p=0.004$) and the %HGT>7.8 ($p=0.036$), which reached statistical significance [TABLE 1] [FIGURE 1].

CONCLUSIONS

The probability of insulin independence after islet transplantation is 75% at 1 year [6] [3]. With time, most patients develop graft dysfunction requiring the reintroduction of exogenous insulin in approximately 60% of the patients by the second year [6] [3]. The early detection of graft dysfunction could facilitate the identification of underlying causes and guide in the management of transplanted patients, especially if anti-rejection therapies become available.

In this study we found that glucose variability and %HGT>7.8 determined by CGMS, can be useful early indicators of graft dysfunction. It is important to note that when the threshold for hyperglycemia was set at 7.8 mmol/L we were able to detect a significant difference between time points A and B by the CGMS recordings (%HGT>7.8). The same could not be detected by setting the threshold at 10 mmol/L by CGMS (%HGT>10) in these patients. Given our results, a threshold of 7.8 mmol/L appears to be better for early detection of graft dysfunction. Our results show that %HGT>7.8 obtained from the CGMS recordings is a better tool to detect early graft dysfunction than capillary blood glucose measurements (%CBG>7.8). The possible explanations for this are the decreased number of determinations performed as time progresses (4 instead of 7 finger sticks per day), but also the capability of the CGMS to detect the post-prandial glucose excursions which can be missed by capillary blood glucose measurements. One limitation of our study is its small sample size. Further studies with a larger population and control groups will help validate these observations.

It is conceivable that in the future the use of real time continuous glucose monitoring technologies will further aid in the early detection of graft dysfunction.

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FIGURE 1.

Increase in glucose variability and percentage time spent in hyperglycemia > 7.8 mmol/L (% HGT>7.8) from time point A (5 to 9 months before dysfunction) to time point B (2 to 3 months before dysfunction).

TABLE 1

Results obtained from the different metabolic parameters at time points A and B and their significance. (NS: Not Statistically Significant)

Parameter	Time point A *	Time point B *	P value
HbA1c	5.8%	6%	0.23 (NS)
C-peptide	1.6 ng/ml	1.8 ng/ml	0.29 (NS)
CPGR	1.6	1.5	0.63 (NS)
90 minute glucose	7.7 mmol/L	8.3 mmol/L	0.48 (NS)
%CBG >7.8	13.2%	9.8%	0.33 (NS)
% HGT >10	1%	3%	0.39 (NS)
%HGT >7.8	11 %	22 %	0.036
Glucose Variability	1.1 mmol/L	1.6 mmol/L	0.004

* Time point A(5 to 9 months before dysfunction)

* Time point B (2 to 3 months before dysfunction)