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ORIGINAL ARTICLE

Early postoperative continuous glucose monitoring in pancreas transplant recipients

Shruti Mittal,[1,2] Rachel H. Franklin,[3] Caterina Policola,[4] Edward Sharples,[1] Peter J. Friend[1,2,5] and Stephen C. L. Gough[3,5]

1 Oxford Transplant Centre, Oxford University Hospital NHS Trust, Oxford, UK
2 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK
3 Oxford Centre for Diabetes, Endocrinology and Diabetes, University of Oxford, Oxford, UK
4 Dipartimento di Endocrinologia e Malattie del Metabolismo, Università Cattolica Del Sacro Cuore, Rome, Italy
5 NIHR Biomedical Research Centre, Oxford, UK

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Correspondence
Shruti Mittal, Oxford Transplant Centre, Churchill Hospital, Old Road, Headington, Oxford OX3 7LE, UK.
Tel.: 01865 857 290;
fax: 01865 857 213;
e-mail: shruti.mittal@gtc.ox.ac.uk

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Summary

Continuous glucose monitoring (CGM) is used in people with type 1 diabetes to help with insulin treatment regimens. Its value in whole-organ pancreas transplantation (PT) is largely unknown. This study aimed to use CGM to assess the metabolic profile of pancreas transplant recipients in the early post-transplant period. We studied CGM data in 30 PT recipients and related findings to an early oral glucose tolerance test (OGTT). Complete data were available for 26 recipients. Seven days after a PT, normoglycaemia was present 77.9% of the time. Hypoglycaemic events (glucose <3.9 mmol/l) occurred in 10 of 26 (38.5%) of the cohort, but were infrequent (present 1.4% of the time). Hyperglycaemia (glucose >7.8 mmol/l) was present for 20.7% of the study period and correlated with a diagnosis of abnormal glucose tolerance. Whilst normoglycaemia is successfully achieved for the majority of the time after PT, hypoglycaemia can occur. Hyperglycaemia is more common and correlates well with the early postoperative OGTT, which is associated with graft failure. CGM is easier to perform and provides 24-h data that could inform clinical decision-making in patients in the postoperative period.

Introduction

Pancreas transplantation (PT) is an established treatment for people with diabetes but medium-term attrition of transplants is high [1]. Effective early markers of graft dysfunction are lacking, and simple measures of blood glucose do not detect graft dysfunction early enough for therapeutic intervention [2]. We have shown recently that abnormal glucose tolerance in the first weeks post-transplant is associated with later graft failure, and the oral glucose tolerance test (OGTT) can be used to identify recipients at highest risk [3]. However, the OGTT is inconvenient and uncomfortable for patients, and time-consuming for medical, nursing and laboratory staff. In many centres, an OGTT test may have been preceded by many days of frequent finger-prick testing. However, little is known about the detailed 24-h metabolic profile occurring in the early post-transplant period. Continuous glucose monitoring (CGM) has been used to assess the effect of interventions in people with diabetes [4] and monitor glucose levels in complex patient groups [5,6]. This study aimed to use CGM to assess the 24-h metabolic profile of pancreas transplant recipients in the early post-transplant period and to examine how these profiles relate to glucose tolerance.

Methods

Pancreas transplantation was performed according to a standardized clinical protocol with systemic venous drainage and enteric exocrine drainage. Donors and recipients were matched according to national organ allocation guidelines. All recipients followed a standard immunosuppression

protocol comprising alemtuzumab induction and tacrolimus and mycophenolate maintenance. Trough tacrolimus levels were maintained between 8 and 12 mg/l, and mycophenolate levels were not monitored. No steroids were used as part of the routine maintenance immunosuppression protocol, nor were steroids used as an acute treatment in any patient in this series.

As part of clinical protocol, all pancreas transplant recipients underwent an OGTT prior to discharge. Serum samples were taken for glucose at baseline and 2 h after a 75-g glucose solution drink. Recipients were categorized as having normal or abnormal glucose tolerance according to WHO criteria [7].

iPro™ 2 CGM probes (Medtronic Ltd, Watford, UK) were prospectively applied to 30 consecutive pancreas transplant recipients between August 2013 and May 2014 at a single centre. Probes were applied on day 7 post-transplant and remained *in situ* for 7 days, or until the patient was discharged. The probe was inserted subcutaneously to the anterior abdominal wall and secured. Readings were taken by the probe and blinded to patient and clinicians. Patients were supplied with a glucose meter for correlation with finger-prick readings. Patients were asked to eat and drink as normal, and to keep a food diary detailing intake.

Hyperglycaemia was managed according to clinic protocol, with clinical decisions based on finger-prick glucose and OGTT findings. Hyperglycaemia and abnormal glucose tolerance were investigated with radiological imaging to assess for underlying thromboses, which were treated if discovered with anticoagulation. Insulin therapy was not used in any participants in this series.

For each participant, 7-day data were analysed. CGM readings were analysed for excursions from the normal range (3.9–7.8 mmol/l, as defined by ADA guidelines [8]). Profiles were compared by type of transplant using the independent samples Mann–Whitney *U*-test, and by OGTT result using the independent samples Kruskal–Wallis test with post hoc analysis of significant values ($P < 0.05$). Receiver operating characteristic (ROC) analysis was performed for correlations between CGM profiles and OGTT result. Normal and abnormal OGTT groups were compared for differences in median trough tacrolimus level using the Fisher's exact test. CGM readings were correlated with finger-prick glucose readings and clinical outcomes. All analyses were performed in SPSS (IBM SPSS Statistics 20, Armonk, NY).

Results

Thirty prospective pancreas transplant recipients were included in the analysis. Three iPro probes failed to record any readings, and one probe was inadvertently removed at return to the operating theatre. Data were therefore available for 26 recipients, including 22 simultaneous pancreas–kidney transplant (SPK) and four PTA. The iPro device was on average inserted on day 7 postoperatively and remained *in situ* for an average of 6.2 days.

Comparison by transplant type

The characteristics of the CGM profile are displayed in Table 1 and were comparable for the SPK ($n = 22$) and PTA ($n = 4$) groups, in terms of demographics, CGM and OGTT parameters. During the period of monitoring, the transplant recipients were within the normoglycaemic range for 77.9% of the time and there were no significant differences between the SPK and PTA groups. Of note, although mild hypoglycaemic episodes (blood glucose <3.9 mmol/l), occurred in 10 of 26 (38.5%) pancreas transplant recipients, low excursions were brief (1.38% of study time below 3.9 mmol/l [8]) and resolved spontaneously. Four of 10 hypoglycaemic episodes were below 3.1 mmol/l. No symptomatic hypoglycaemic events were observed. The frequency of hyperglycaemic episodes was, however, more common (20.69% of study time >7.8 mmol/l), with small, non-significant differences between the SPK and PTA groups. CGM data were compared with data from regular finger-prick glucoses, as shown in Table 2. Finger-prick estimations approximated CGM data, although highest glucose readings were underestimated and hypoglycaemic events were often missed.

Comparison by glucose tolerance

OGTT data were available for 23 pancreas transplant recipients. Eleven of 23 (47.8%) pancreas transplant recipients

Table 1. Demographics and continuous glucose monitoring profile of whole cohort and for each transplant type.

	Whole cohort ($n = 26$)
Recipient age (years)	43.7 ± 10.1
Days post-transplant (days)	7.0 ± 1.0
Highest glucose reading (mmol/l)	10.43 ± 2.43
Lowest glucose reading (mmol/l)	4.07 ± 0.88
Mean glucose value (mmol/l)	6.69 ± 1.20
Total number of high excursions	8.19 ± 7.87
Total number of low excursions	0.69 ± 1.09
AUC glucose above 7.8 mmol/l	0.31 ± 0.54
AUC glucose below 3.9 mmol/l	0.01 ± 0.02
Time above 7.8 mmol/l (%)	20.69 ± 26.94
Time in normal range (%)	77.92 ± 27.01
Time below 3.9 mmol/l (%)	1.38 ± 2.59
OGTT	
0 h	5.68 ± 0.96
2 h	8.18 ± 2.73

Values are expressed as mean ± standard deviation. AUC, area under the curve; OGTT, oral glucose tolerance test.

Table 2. Comparison of finger-prick (BM) and continuous glucose monitoring (CGM).

	NGT (n = 11)		IGT (n = 10)		DGT (n = 2)	
	BM	CGM	BM	CGM	BM	CGM
Highest glucose reading (mmol/l)	8.6	9.3	10.8	11.8	12.4	13.6
Lowest glucose reading (mmol/l)	4.7	4.2	5.3	3.9	4.2	4.0
Mean glucose value (mmol/l)	6.4	6.0	7.9	7.3	7.9	8.0
Time above 7.8 mmol/l (%)	4.8	4.5	47.8	38.2	37.5	47.5
Time in normal range (%)	95.0	94.1	56.1	59.8	59.0	52.0
Time below 3.9 mmol/l (%)	0	1.4	0	2.0	3.6	0.1

had normal glucose tolerance (NGT), 10 of 23 (43.5%) had impaired glucose tolerance (IGT), and 2 of 23 (8.7%) had diabetic glucose tolerance (DGT). The median trough tacrolimus level was 7.9 mg/l (IQR 6.62–10.41). There was no significant difference in tacrolimus level between those with normal and abnormal glucose tolerance (P = 0.684). The mean continuous glucose profiles were compared by glucose tolerance category (Fig. 1a). No significant difference was seen in the frequency or duration of hypoglycaemic episodes between glucose tolerance groups (Table 3). Hyperglycaemic excursions were more frequent and reached higher levels in recipients with IGT and DGT compared with recipients with NGT. Those with IGT and DGT spent a comparable percentage of the study period above the normal range, which was significantly higher than those with NGT (P = 0.012). Those with NGT spent a significantly higher percentage of time within the normal range compared with those with IGT and DGT (94.2% NGT vs. 59.8% IGT vs. 52.0% DGT, P = 0.008; Fig. 1b). ROC curve analysis showed that abnormal glucose tolerance was most associated with percentage time in hyperglycaemia (area under curve 0.86, CI 0.67–1.00; P = 0.004). Abnormal glucose tolerance was predicted with sensitivity of 83.3% and specificity of 100% for time spent in hyperglycaemia of 10.5% (Fig. 2).

Relationship with clinical outcome

Five of 26 (19.2%) patients had early clinical complications: 3 of 26 (11.5%) suffered graft pancreatitis, one of which

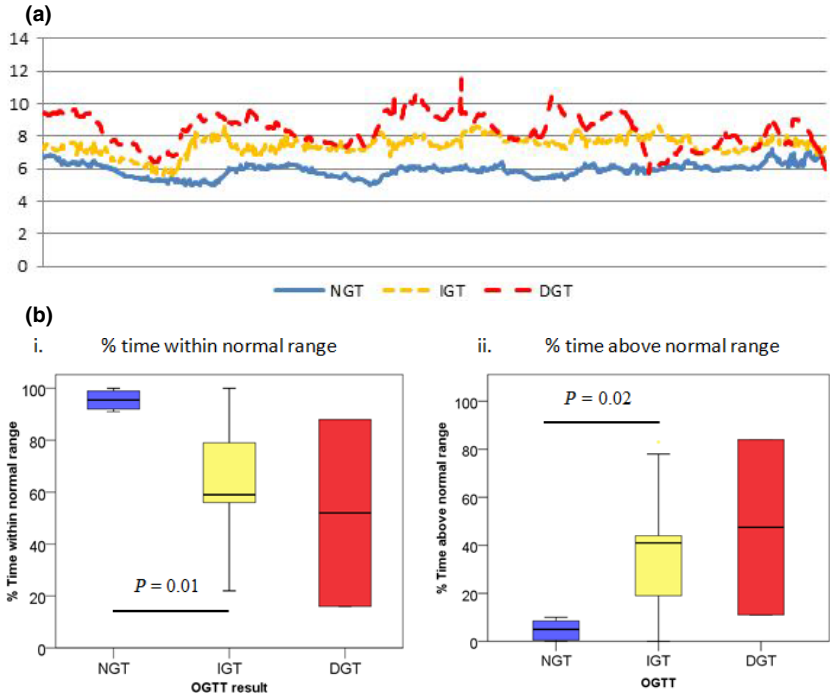

Figure 1 (a) Average continuous glucose profile for pancreas transplant recipients with normal glucose tolerance (NGT): impaired glucose tolerance (IGT) and diabetic glucose tolerance (DGT). (b) Box plot depicting percentage of study time spent (i) within normal range (3.9–7.8) and (ii) above normal range (>7.8 mmol) for recipients with NGT, IGT and DGT as compared using independent samples Kruskal–Wallis test.

Table 3. Demographics and continuous glucose monitoring profile of whole cohort and for each transplant type.

	NGT (n = 11)	IGT (n = 10)	DGT (n = 2)	P-value
Recipient age (years)	40.1 ± 8.9	47.0 ± 11.1	37.0 ± 7.1	0.305
Days post-transplant (days)	7.1 ± 1.4	7.3 ± 0.7	7.0 ± 0.0	0.526
Highest glucose reading (mmol/l)	9.25 ± 1.57	11.75 ± 2.39	13.60 ± 1.56	0.025
Lowest glucose reading (mmol/l)	4.15 ± 0.75	3.93 ± 1.20	3.95 ± 0.35	0.603
Mean glucose value (mmol/l)	5.99 ± 0.57	7.34 ± 1.20	8.05 ± 2.19	0.019
Total number of high excursions	4.82 ± 4.64	13.3 ± 9.57	10.0 ± 0.0	0.056
Total number of low excursions	0.13 ± 1.35	0.90 ± 0.99	0.50 ± 0.71	0.621
AUC glucose above 7.8 mmol/l	0.03 ± 0.03	0.54 ± 0.53	1.60 ± 1.41	0.010
AUC glucose below 3.9 mmol/l	0.01 ± 0.02	0.01 ± 0.02	0.0 ± 0.0	0.417
Time above 7.8 mmol/l (%)	4.45 ± 4.12	38.2 ± 27.89	47.5 ± 51.62	0.012
Time in normal range (%)	94.18 ± 5.79	59.8 ± 27.33	52.0 ± 50.91	0.008
Time below 3.9 mmol/l (%)	1.36 ± 3.11	2.00 ± 2.58	0.05 ± 0.71	0.420

NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DGT, diabetic glucose tolerance; AUC, area under the curve.

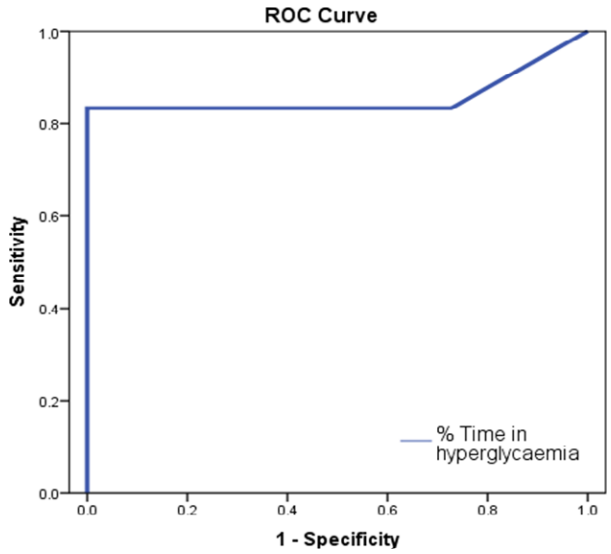

Figure 2 Receiver operating curve analysis of percentage time in hyperglycaemia and abnormal oral glucose tolerance test result.

resulted in graft pancreatectomy, 2 patients had radiologically diagnosed partial venous thrombosis relating to the pancreas graft treated with anticoagulation, and 1 of 26 (3.8%) had delayed kidney graft function. All of the patients with complications, except the patient who underwent pancreatectomy, had episodes of hyperglycaemia and IGT or DGT. 8 of 12 (66.6%) patients with abnormal glucose tolerance had an uneventful early clinical course. All patients had 6-month follow-up clinical outcome data, and 16 had 1 year clinical outcome data. The remaining 25 grafts were functioning at last follow-up, and all except two had an HbA1c of <5.3%. Two of 25 (8%) had an HbA1c above 6.2% at 1 year postop. Both had shown hyperglycaemia and abnormal glucose tolerance early postoperatively; one patient did suffer graft pancreatitis, and the other had an uneventful clinical course.

Discussion

This is the largest study to examine continuous glucose profiles after PT, and the first to do so early after transplantation period with matched OGTT. As such, we have been able to make several observations. First, minor hypoglycaemia was common and present in over a third of patients. In each patient in whom it occurred, it was, asymptomatic, infrequent, of short duration and resolved spontaneously such that no clinically significant hypoglycaemic events occurred. This supports findings from other groups that, although frequently missed with finger-prick monitoring alone, hypoglycaemic events often occur, resolve spontaneously and are unlikely to have any clinical consequence [9,10].

Second, recipients of SPK and PTA transplants had comparable glucose profiles. A previous study found PTA recipients to have a higher mean glucose concentration when compared to SPK recipients, although acknowledging that the PTA group had a different immunosuppression protocol with higher tacrolimus dosing and steroids, which are likely to have affected glucose control [11].

Third, we have shown that CGM correlates with the OGTT result with recipients displaying excursions above the normal range >10% of a 24-h period likely to display abnormal glucose tolerance. Transplant recipients with NGT demonstrate near normal 24-h glucose profiles, which have been shown to be superior to those seen with intensive insulin therapy [12]. Whilst it is reassuring to see that those with NGT spend 94% of time within normal range, it is notable that those with IGT or DGT spend significantly higher percentage of time above the normal range. We have

recently shown that abnormal glucose tolerance is associated with poor graft survival [3]. The results of the current study clearly show that although the abnormal OGTT is based upon a single time-point blood glucose, subjects with abnormal glucose tolerance spend significant and more prolonged periods of time in the hyperglycaemic range. We know that prolonged periods of hyperglycaemia can induce beta cell toxicity [13], which may well therefore be contributing to poorer long-term graft outcomes and ultimately a higher risk of diabetes-related complications in some of our patients with abnormal glucose tolerance [14]. Lauria *et al.* [11] have previously shown that higher mean glucose concentration was predictive of pancreas graft failure. The data from the present study would add further weight to this notion. Whilst some patients with early hyperglycaemia did have a normal HbA1c at 1-year follow-up, subjects who had high HbA1c at 1 year had shown early hyperglycaemia on CGM.

The authors accept that there are limitations to this study including the relatively small number of subjects in whom there was complete date. Unfortunately, four probes did not yield data sufficient to be used in the analysis; one was accidently dislodged early after its insertion and three failed to register. In addition, OGTT data were not available for three patients. Although detailed longer term graft outcomes are not yet available, and therefore meaningful correlation analysis could not performed, graft attrition rates are known to be highest during the first year post-transplant and the early identification of grafts that are at a risk of failing during this period is likely to be of the greatest benefit. These findings are important, as they identify a marker of glycaemic control previously not utilized in pancreas transplant monitoring, and confirm that CGM can provide detailed data, which need further investigation in a larger follow-up study to identify indices leading to earlier diagnosis of graft failure.

In conclusion, CGM is a feasible, convenient and patient-friendly monitoring tool in the post-transplant setting, negating the need for uncomfortable finger-prick testing and OGTTs, the overall cost of which is not insignificant even when compared to CGM. CGM is easier to perform in the outpatient setting then OGTTs, as patients may forget to fast and ensuring accurate blood sample timings can be challenging. Moreover, it has the advantage of frequent time-point data enabling accurate assessment of hyperglycaemia and potentially more sensitive identification of pancreas transplant recipients at the greatest risk of later graft failure. We recommend CGM for all pancreas transplant recipients post-transplant to identify patients likely to benefit from closer follow-up monitoring and consideration of interventions aimed at optimizing and protecting pancreatic function.

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Authorship

SM, RF, CP, ES, PJF and SCLG: participated in research design. SM, ES, PJF and SCLG: participated in the writing of the paper. SM, RF and CP: participated in the performance of the research. SM, RF, CP, ES, PJF and SCLG: participated in data analysis.

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