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Comparison of glycemic control and variability in patients with type 2 and posttransplantation diabetes mellitus

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ABSTRACT

Aim: Posttransplantation diabetes mellitus (PTDM) is a common complication after renal transplantation leading to increased cardiovascular morbidity and mortality. In subjects with type 2 diabetes (T2DM) increased glycemic variability and poor glycemic control have been associated with cardiovascular complications. We therefore aimed at determining glycemic variability and glycemic control in subjects with PTDM in comparison to T2DM subjects.
Methods: In this observational study we analyzed 10 transplanted subjects without diabetes (Control), 10 transplanted subjects with PTDM, and 8 non-transplanted T2DM subjects using Continuous Glucose Monitoring (CGM). Several indices of glycemic control quality and variability were computed.
Results: Many indices of both glycemic control quality and variability were different between control and PTDM subjects, with worse values in PTDM. The indices of glycemic control, such as glucose mean, GRADE and M-value, were similar in PTDM and T2DM, but some indices of glycemic variability, that is CONGA, lability index and shape index, showed a markedly higher (i.e., worse) value in T2DM than in PTDM (P value range: 0.001–0.035).
Conclusions: Although PTDM and T2DM subjects showed similar glycemic control quality, glycemic variability was significantly higher in T2DM. These data underscore potential important pathophysiological differences between T2DM and PTDM indicating that increased glycemic variability may not be a key factor for the excess cardiovascular mortality in patients with PTDM.

1. Introduction

Posttransplantation diabetes mellitus (PTDM) is a common complication after renal transplantation leading to increased cardiovascular morbidity and mortality as well as reduced graft survival (Sharif & Baboolal, 2012). Indeed, 10%–40% of kidney transplant recipients (KTRs) without prior history of diabetes mellitus develop PTDM (Hecking et al., 2013a; USRDS, 2011). Patients with PTDM develop diabetic complications at a much accelerated rate compared to non-transplanted patients with type 2 diabetes mellitus (T2DM) (Burroughs et al., 2007). The reason for this is largely unknown. Continuous Glucose Monitoring (CGM) provides detailed information about blood glucose levels throughout the day, and possibly facilitates optimal treatment decisions for patients with diabetes (Klonoff, 2005). CGM has also proven helpful in subjects under special circumstances when glycemic patterns are less well understood such as during hemodialysis and in women with gestational diabetes (Chantrel et al., 2014; Secher et al., 2013). Thus, it may be useful also for the study of PTDM.

PTDM is increasingly seen as a diabetes form of its own and shows pathophysiological differences compared to T2DM (Hecking et al., 2013b); as an example, glycemic patterns in PTDM subjects typically show peak glucose levels in the afternoon at least during periods of intermediate and high-dose steroid therapy (Hecking et al., 2012; Yates et al., 2013). Pathophysiologically, an impaired insulin secretion seems to contribute more than decreased insulin sensitivity, when transplanted subjects are compared to individuals with T2DM (Hecking et al., 2013a; Zelle et al., 2013). Few studies have focused on CGM data analysis in renal transplanted subjects. CGM can be helpful in transplant recipients to detect hyperglycemic episodes that would potentially not have been diagnosed using glycated hemoglobin (HbA1c) or fasting plasma glucose alone (Pasti et al., 2013; Rodriguez et al., 2010; Wojtusciszyn et al., 2013). In addition, higher glycemic variability has been linked to increased risks for cardiovascular complications in T2DM, although this link is not well established,

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especially not for macrovascular complications (Smith-Palmer et al., 2014). However, to the best of our knowledge, no studies have so far been performed comparing glycemic patterns in transplant recipients with PTDM to subjects with T2DM. The aims of the present study were to analyze glycemic control quality and variability in renal transplanted subjects both with and without PTDM, and to compare them to a group of non-transplanted T2DM subjects in order to further characterize potential pathophysiological differences between T2DM and PTDM.

2. Methods

2.1. Subjects

We studied 10 transplanted subjects without diabetes (control), 10 transplanted subjects with PTDM, and 8 non-transplanted subjects with T2DM using CGM. PTDM and T2DM subjects were only on oral antihyperglycemic agents as listed in Table 1. At our outpatient department KTRs usually undergo an oral glucose tolerance test (OGTT) at least 6 months after transplantation. A limited number of subjects were offered to undergo CGM. Among 22 KTRs that underwent CGM, 20 subjects were not under therapy with insulin. Of these, 10 had PTDM, whereas 10 were without diabetes according to their OGTT results. PTDM patients did not have a history of diabetes mellitus before transplantation as judged from their medical records. Subjects underwent CGM with measurement of glucose every 5 minutes for a period of 5.9 ± 0.3 days (mean ± SE). T2DM subjects that underwent CGM were recruited from the diabetes outpatient department. For this analysis, we selected 8 T2DM subjects, without history of insulin treatment (similar to the PTDM subjects), and that were mean-matched to the PTDM subjects in terms of mean glucose, BMI, age, and also HbA1c, thus yielding two groups of subjects that were, on average, at similar stage of their diabetic disease. Transplanted subjects underwent CGM 38.5 ± 12.3 months after transplantation. At the time of CGM the mean duration of T2DM had been 9.8 ± 2.5 years. T2DM was not due to treatment with corticosteroids. This observational study was approved by the local ethics committee (EK #566/2009), and subjects provided informed consent to the study.

Table 1
Basic characteristics of non-diabetic transplanted subjects (control), transplanted subjects with PTDM, and non-transplanted subjects with T2DM.

	Control ($n = 10$)	PTDM ($n = 10$)	T2DM ($n = 8$)
Basic characteristics			
Age (years)	60.4 ± 2.9	57.6 ± 2.2	59.6 ± 1.7
BMI (kg/m^2)	26.9 ± 1.3	28.9 ± 1.3	28.9 ± 2.6
HbA1c (%)	6.0 ± 0.1	6.5 ± 0.3	6.9 ± 0.2[a]
Lipids			
Cholesterol (mmol/l)	5.98 ± 0.39	5.19 ± 0.22	4.85 ± 0.82[a]
HDL (mmol/l)	1.31 ± 0.09	1.23 ± 0.11	1.78 ± 0.36
LDL (mmol/l)	3.64 ± 0.35	2.79 ± 0.14	2.32 ± 0.47[a]
Triglycerides (mmol/l)	2.29 ± 0.35	2.59 ± 0.33	1.66 ± 0.31
Antidiabetic therapy			
Metformin (n)	–	–	8
DPP-4 inhibitor (n)	–	3	5
Sulfonylurea (n)	–	1	–
Immunosuppressive therapy			
Cyclosporine A (n)	1	3	–
Tacrolimus (n)	9	7	–
Steroid therapy			
Prednisone dose (mg)	4.5 ± 1.1	4.25 ± 1.7	–

Data are presented as mean ± SE. For the therapies, the number of subjects is reported.
[a] Significant difference ($P < 0.05$) between T2DM and control.

2.2. Equipment

The CGM device used in this study was the iPro 2 system (Medtronic, Inc, USA), consisting of an intradermal glucose sensor that measures interstitial glucose levels. For calibration, subjects had to measure capillary blood glucose at least 4 times daily using a hand-held glucometer (ContourTS, Bayer Austria GmbH). Subjects did not see the results of the CGM measurements. Retrospective calibration and analysis of the stored data were performed by medical staff after the devices had been removed.

2.3. Calculation of indices of glycemic control quality and variability

For a detailed analysis of the glucose data we assessed several indices of glycemic control quality and glycemic variability. The indices of glycemic control quality describe to what extent the glucose data tend to remain near a target value or in a target range. There are both basic indices of descriptive statistics, and more complex indices. As regard the former, the calculated indices are glucose mean, mean normalized to the standard deviation, maximum, minimum, 50-th percentile (median), percentage of glucose values in a target range (4.4–11.1 mmol/l, i.e., 80–200 mg/dl), and below and above a target value (4.4 and 11.1 mmol/l, respectively). It should be noted that 4.4 and 11.1 mmol/l are somewhat arbitrary thresholds, but they have been used in many studies (Rodbard, 2009a). The more complex indices are:

i) GRADE (Glycemic Risk Assessment Diabetes Equation) (Hill et al., 2007): glucose values are transformed to yield a continuous curvilinear response with a nadir of 5.5 mmol/l and high adverse weighting to hyperglycemia and hypoglycemia: $GRADE = 425 \times [\log_{10}[\log_{10}(Gluc_n)] + 0.16]^2$, with $Gluc_n$ in mmol/l; then, average value is taken;
ii) M-VALUE (Schlichtkrull et al., 1965): it is a weighted average of the glucose values, with progressively larger penalties for more extreme values: $M\text{-}VALUE = |10 \times \log_{10} Gluc_n/IGV|^3$, where IGV is the ideal glucose value, typically assumed, as in this study, equal to 6.7 mmol/l (120 mg/dl); again, average value is then taken;
iii) Hypoglycemia index (Rodbard, 2009a) is the weighted average of hypoglycemic values; if blood glucose value is lower than a given threshold, the formula for the index is: $Hypo\_index = (LLTR - Gluc_n)^{2.0}/30$, with $Gluc_n$ and LLTR in mg/dl (typically, LLTR = 80 mg/dl);
iv) Hyperglycemia index (Rodbard, 2009a) is the weighted average of hyperglycemic values; if blood glucose value is higher than a given threshold, the formula for the index is: $Hyper\_index = (Gluc_n - ULTR)^{1.1}/30$, with $Gluc_n$ and ULTR in mg/dl (typically, ULTR = 140 mg/dl);
v) IGC (Index of Glycemic Control) (Rodbard, 2009a) is the sum of Hyperglycemia Index and Hypoglycemia Index;
vi) LBGI (Low Blood Glucose Index) (Kovatchev et al., 1997): transformation that normalizes the blood glucose scale: $LBGI = 1.509 \times [(\log_e(Gluc_n))^{1.084} - 5.381]$, for blood glucose values less than 112.5 mg/dl; then, a risk value is assigned to each blood glucose reading as follows: $Risk(LBGI) = 10 \times LBGI^2$; finally, average value is taken;
vii) HBGI (High Blood Glucose Index) (Kovatchev et al., 1997): similarly to LBGI, a transformation to normalize the blood glucose scale, for blood glucose values higher than 112.5 mg/dl: the expression of HBGI is the same as for LBGI; and
viii) ADRR (Average Daily Risk Range) (Kovatchev et al., 2006): it is the sum of LBGI and HBGI, calculated with the minimum and the maximum glucose value, respectively.

The indices of glycemic variability measure to what extent CGM data tend to oscillate: the higher the variability, the higher the value of such indices. Some basic indices of this type are the glucose standard