Assessing Glycaemic Control in Maintenance Haemodialysis Patients with Type 2 Diabetes

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Objective: Optimising glycaemic control in diabetic patients on maintenance haemodialysis (HD) requires its accurate assessment. We hypothesize that 1) 48-hour continuous glucose monitoring (CGM) provides additional, clinically relevant, information to that provided by the HbA1c measurement and 2) glycaemic profiles differ significantly between day on and day off dialysis.

Research Design and Methods: 48-hour CGM was performed using GlucoDay®S in 19 type 2 diabetic HD subjects capturing consecutive 24-hour periods on and off HD. Energy intake was calculated using food diaries. HbA1c was assayed by an HPLC method.

Results: CGM data was available for 17 subjects (13 male), aged (mean, range) 61.5 yrs (42 - 79) and diabetes duration of 18.8 years (4 - 30). The 24 hour CGM area under the glucose curve and 24-hour mean glucose values were significantly higher during the day off dialysis than on dialysis (5932.1 ± 2673.6 vs. 4694 ± 1988.0mmol.min⁻¹.l⁻¹, p=0.022 and 12.6 ± 5.6mmol.L⁻¹ vs. 9.8 ± 3.8mmol.L⁻¹, p=0.013, respectively), independent of energy intake. Asymptomatic hypoglycaemia occurred in 4 subjects, 3 within 24 hours of dialysis and the glucose nadir in 14 subjects occurred within 24 hours of dialysis.

Conclusions: Glucose values are significantly lower on dialysis than non-dialysis days despite similar energy intake. The risk of asymptomatic hypoglycaemia was highest within 24 hours of dialysis. Physicians caring for these patients need to be aware of this phenomenon and consider enhanced glycaemic monitoring following a haemodialysis session. Thus, CGM provides additional glycaemic information to the HbA1c that is potentially relevant to clinical management.
Diabetic nephropathy is the leading cause of end-stage renal failure (ESRF) [1] representing 30-45% of the UK and USA [2] long-term maintenance haemodialysis (HD) population. The patients typically are elderly type 2 diabetic patients with established micro and macrovascular disease [3]. Hypoglycaemia is common due to impaired renal gluconeogenesis, malnutrition and the increased half-life of insulin and hypoglycaemic agents [4]. The annual mortality among diabetic HD patients is high, predominately from cardiovascular disease (CVD) [2].

Intensive glycaemic management delays progression of microvascular disease [5-8] and improves malnutrition [9], however large randomized controlled trials show no mortality benefit in high risk groups with CVD [7] [10]. Hypoglycaemic events increase with intensive treatment and in the presence of CVD can cause fatal dysrhythmia [11]. UK diabetic guidelines advise against intensive treatment aimed at lowering HbA1c levels below 6.5% [12] while American guidelines caution against values below 7% [13]. No evidence-based guidelines for the glycaemic targets for diabetic patients with ESRF on long-term maintenance HD are available.

In patients without ESRF the HbA1c value is routinely used to assess long-term glycaemic control and assays are standardized to those used in the Diabetes Control and Complication Trial (DCCT)[14]. There is a strong correlation between HbA1c values and the preceding two-three months’ weighted mean glucose values [14]. The validity of the HbA1c measurement in ESRF and HD patients depends on the methodology [15]. A number of factors may influence the assay including altered red cell (RBC) life-span, metabolic and mechanical factors [16]. Potential metabolic factors are interference from carbamylated haemoglobin formed in uraemia and acetylated haemoglobin formed from long term aspirin use [17].

A limitation of the HbA1c value in patients on HD is that it is non-informative on how dialysis may affect glycaemic control on the days on and off dialysis. In the UK, maintenance HD is typically given in a hospital setting three times a week, with sessions lasting 4-5½ hours. The CGM devices that measure glucose every three minutes using a biosensor and a subcutaneous micro-bore cannula are by contrast ideally suited to examine the effect of dialysis on glucose profiles over a 48 hour period.

The present study tests the hypothesis that 1) 48-hour CGM provides additional, clinically relevant, information to that provided by the HbA1c measurement in HD patients 2) 24-hour glucose profiles are different on the day that includes a dialysis session compared with a day that does not.

**RESEARCH DESIGN AND METHODS**

**Ethics.** The study was approved by the Hammersmith Hospital Research Ethics Committee and written informed consent obtained (Registration Number: 2002/6260).

**Study objectives.** To compare glucose profiles from days on and off HD using 48 hour CGM in type 2 diabetic patients. To examine the association between self-reported food intake and the CGM values. To evaluate glycaemic assessment obtained using 48-hour CGM in type 2 diabetic maintenance HD patients.

**Subjects.** Nineteen (14 male) Type 2 diabetic subjects were recruited from the maintenance HD program at Imperial College Kidney and Transplant Institute (ICKTI). Subjects were dialysed against a <2 mmol.L⁻¹ glucose containing dialysate for 4-5½ hours either during the morning, afternoon or early evening. Inclusion criteria were a stable
haemoglobin (Hb) level, defined as <10% change in Hb value and no blood transfusion in the preceding 3 months, a stable dose of erythropoietin and no haemoglobinopathy. History of cardiovascular disease was established as documented ischaemic heart disease (history of myocardial infarction, revascularisation procedure or angiographically proven coronary disease), cerebrovascular disease (history of cerebrovascular accident or transient ischaemic attack) or peripheral vascular disease (history of amputation due to gangrene, revascularisation procedure or angiographically or doppler proven peripheral vascular disease).

**Blood samples.** Blood samples were taken for HbA1c, haemoglobin, albumin and urea at the start of dialysis.

**Continuous glucose monitoring.** Day 1. Subjects attended ICKTI and prior to starting dialysis a GlucoDay®S CGM device from A.Menarini Diagnostics (Florence, Italy) [18] was fitted and placed in a pouch to be worn around the waist. The CGM biosensor was calibrated retrospectively using capillary blood glucose testing as advised by the manufacturer.

Day 3. (48 hours later) Subjects attended ICKTI and prior to their dialysis session the CGM device was removed. The data was downloaded to a computer using dedicated software (GlucoDay®S Data Presentation Software).

**Exclusion criteria.** Exclusion criteria were prospectively defined as: Type 1 diabetes, inter current illness, changes to medication regimen during the monitoring period or occurrence of prolonged hypoglycaemia.

**Patient diaries.** On Day 1 subjects were given a 48-hour diary to record the exact time and amount of food, drink and medications taken during the entire CGM monitoring period, together with any episodes of symptomatic hypoglycaemia and all capillary blood glucose results.

**Laboratory analysis.** The HbA1c measurements were performed in the hospital’s clinical biochemistry laboratory using a DCCT-aligned HA-8160 HbA1c auto-analyser (A.Menarini Diagnostics). This analyzer is not subject to interference by urea as this reverse-phase cation exchange high-performance liquid chromatography method provides good separation of HbA1c from carbamylated HbA1.

The haemoglobin measurements were performed in the hospital’s routine haematology laboratory using a XE2100 auto-analyzer (Sysmex, Toa Medical Electronics, Kobe, Japan) running a variation of the CyMet-haemoglobin absorbtimetric method. Serum urea and serum albumin tests were performed on an Architect ci8200 multi-channel analyser (Abbott Diagnostics, Illinois, USA).

**Assessment of glycaemic control.** The 48-hour glucose profiles were quantified using dedicated software (GlucoDay®S Data Presentation Software) as the area under the 3-minute glucose curve (AUC) and the mean glucose value. The time periods studied were the first 24-hour period starting the first hour of dialysis (day on dialysis) and the 24-hour period ending one hour prior to the next dialysis session (day off dialysis). The 6-hour nocturnal periods from midnight to 6:00 a.m. for each of these 24-hour periods were also examined in order to examine the effect of dialysis. Hypoglycaemia, defined as a continuous glucose reading <2.5 mmol.L⁻¹ for more than 30 minutes, was identified from the CGM profiles. Subjects were questioned regarding symptoms of hypoglycaemia at the end of the CGM period.

**Dietetic analysis.** Completed food diaries were checked during a dietary consultation with a registered dietitian. Food portions were verified using a pictorial food atlas (MAFF Publications 1997). Comparisons of dietary intake during the 24-
hour periods on and off dialysis were performed by a data-analyst blinded to the study using the Dietplan 6 software package (Forestfield Software). Daily energy requirement was calculated at 30-35 kCal/kg ideal body weight (Renal Association 2002).

**Statistical analysis.** The CGM data was exported into SPSS version 14 software (SPSS for Windows, Release 14.0.0 [5 September 2005], LEAD Technologies, Inc.) and tested for normality using the Shapiro-Wilk test.

All normally distributed data is expressed as mean and standard deviation (SD) and non-normally distributed data as median and range. All comparisons of the glycaemic profiles and dietary intake between days on and off dialysis was analysed using paired Student’s t-tests.

Linear regression analysis was used to assess the relationship between laboratory HbA1c, and weekly EPO dose, serum urea and serum albumin.

The level of significance was defined as p<0.05.

**RESULTS**

Nineteen (14 male) subjects were recruited, two were subsequently excluded; one due to repeated hypoglycaemia during both monitoring periods and one due to CGM technical failure.

The age, duration of DM and years of dialysis [mean ± SD, (range)] of the 17 (13 male) subjects included were 61.5 yrs ± 8.8 yrs, (42-79); 18.8 ±7.6 yrs (4-30) and 4± 2.6 yrs (0.5-10.2), respectively. Previous CVD history, diabetic medications, erythropoietin dose, HbA1c, haemoglobin and urea values are given (Table 1).

**HbA1c values.** The HbA1c (Mean ±SD) was 6.9 ± 1.2%, (range 5.1-9.2 %), with 7 subjects having an HbA1c of ≥6.5% (Table 1). Linear regression analysis between HbA1c and erythropoietin dose, serum albumin and urea were not significant, (r²=0.17, p=0.0995; r²=0.161, p=0.536 and r²=0.163, p=0.533, respectively.)

**Haemoglobin values.** The mean haemoglobin was 12.4 ± 1.6g.L⁻¹ (range 9.3-15.1)

**Analysis of glycaemic profiles.** The 24-hour AUC glucose values and mean 24-hour CGM data were significantly higher on the day off dialysis than the day on dialysis (5932.1 ± 2673.6 vs. 4694 ± 1988mmol.3min.L⁻¹, p=0.022 and 12.6 ± 5.6mmol.L⁻¹ vs. 9.8 ± 3.8mmol.L⁻¹, p=0.013, respectively), Figure 1. The difference in the 24-hour mean glucose levels for the day off dialysis to the day on dialysis ranged from -2.1 to 10.4mmol.L⁻¹.

The AUC glucose profiles and the mean glucose values for the 6-hour nocturnal period from midnight to 6 am were significantly higher for the second than the first night (1541 ± 834 vs. 1137 ± 529 mmol.3min.L⁻¹, p<0.05; and 12.9 ± 7.0 vs. 9.5 ± 4.4 mmol.L⁻¹ p<0.05, respectively). With a median 6-hour mean nocturnal glucose difference of 4.2mmol.L⁻¹(range -8.5 to 17.1mmol.L⁻¹), Figure 2.

**Analysis of hypoglycaemia.** Four of the 17 subjects had CGM recordings of below 2.5mmol.L⁻¹ for more than 30 minutes; in 3, this occurred in the first 24-hour monitoring period. Examination of individual CGM profiles showed that 14/17 subjects reached their glucose nadir (range 1.38-9.81mmol.L⁻¹) within the first 24 hours, with 10/17 having their lowest reading within 12 hours of starting dialysis. No subject reported any episode of symptomatic hypoglycaemia.

**Analysis of the food diaries.** Two subjects failed to complete their 48-hour food diaries (subjects 6 and 15). Analysis of the 15 completed diaries showed no significant difference between recorded dietary intakes for the day on dialysis and the day off dialysis (1636 ± 603kCal vs. 1702 ± 559kCal, respectively, p = 0.596). There was no trend
towards greater food intake on either day, with 7 subjects recording a greater calorie intake during the day on dialysis versus 8 the day off dialysis. The timing of the dialysis shift did not appear to influence the energy intake (data not shown).

The total energy intake for each subject was significantly lower, both on dialysis days (mean 1636kCal/day) and off dialysis days (mean 1702kCal/day), than the estimated mean energy requirement (2000kCal/day), p = 0.01, (data not shown).

**Medications.** No subject recorded a change in frequency or dosing of medications, including insulin, on the two days.

**CONCLUSIONS**

The need to balance glycaemic targets to avoid hypoglycaemia with the risks of microvascular disease from hyperglycaemia requires accurate glycaemic assessment. This is especially so for diabetic patients on maintenance HD who have a high prevalence of microvascular and macrovascular disease and an increased risk of asymptomatic hypoglycaemia during HD [19]. Continuous subcutaneous glucose monitors are ideally suited for diabetic patients on HD, as unlike the HbA1c they can examine short-term glycaemic changes around the time of dialysis and are unaffected by urea, RBC life-span and RBC production.

The need to set the appropriate glycaemic targets for type 2 diabetic patients with a high CVD risk was highlighted by the Action to Control Cardiovascular Risk in Diabetes study (ACCORD) [7] and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [8] randomized controlled trials. These studies recruited subjects at high risk of CVD and neither showed any CVD benefit from targeting HbA1c levels below 6.5% and 7%, respectively. The ACCORD study actually showed a small increase in overall mortality when targeting HbA1c below 6.5%. That low HbA1c levels may not confer survival benefit in ESRF was also suggested by a one year follow-up study of 23,000 American diabetic subjects [20]. By contrast good glycaemic control prior to dialysis does appear to have some CVD benefit [21]. Thus, it may be necessary for HbA1c targets originally based on low CVD non-CKD populations to be re-evaluated for diabetic haemodialysis patients.

The HbA1c is a measure of the irreversible non-enzymatic glycation product of one or both NH2-terminal valines of the beta-hemoglobin chain. In ESRF the HbA1c assay can be affected by interference from carbamylated hemoglobin formed from urea-derived isocyanate that accumulates in uraemia [22]. However advances in reverse-phase cation exchange HPLC analyzers, as used in this study, allow for greater haemoglobin peak separation [23]. Shortened RBC life-span or increased RBC production [16] can occur in ESRF and both can falsely lower HbA1c values by reducing the RBC glycaemic exposure time. However, a study of 23 HD patients on regular erythropoietin therapy and with stable haemoglobin values, concluded that it was the ambient glucose concentration rather than RBC life-span that was the major determinant, as no correlation between RBC life-span and HbA1c measured by either immunoassay or HPLC was shown [24]. Starting or increasing erythropoietin treatment could, by increasing RBC production, falsely lower HbA1c values by increasing the proportion of younger RBCs and thereby reducing glucose exposure time. In the present study all subjects had stable haemoglobin values and their erythropoietin doses had remained constant over the preceding 3 months.

Furthermore, the HbA1c value may be less informative in the type 2 diabetic maintenance HD population and may be less easily translated into mean glycaemic values...
than in other populations. The ADAG (A1c Derived Average Glucose Study Group) investigators recently reported (25) that HbA1c levels can be converted to average glucose levels in T2DM. However, CKD patients were excluded from this study and it is possible that the metabolic fluctuations seen around haemodialysis may weaken the relationship between HbA1c and average glucose. One of the alternative methods of glycaemic assessment to HbA1c is CGM.

The present study showed over a 2 day period that the GlucoDay®S CGM device recorded significantly higher glucose profiles on the day off dialysis than the day on dialysis.

The CGM glucose values during the first 24-hour monitoring period (day on dialysis), including the six-hour nocturnal period were significantly less than the second 24-hour monitoring period. During the hours of midnight to 6.00am, the only common time all subjects were resting and not eating, the magnitude of this difference ranged from -8.5 to 17.1mmol.L⁻¹, with a median difference of 4.2mmol.L⁻¹. These differences in glucose profiles were not explained by the difference in 24-hour energy intake, changes in medication or dialysis shift. However, there are potential limitations over the accuracy of the food diaries, as data was collected over 48 hours only and was self-reported. The food data did highlight that all subjects were likely to be malnourished as they consumed less than their recommended intake.

The CGM data also showed that 4 subjects had hypoglycaemia, <2.5mmol.L⁻¹ over 30 minutes or more, and that this occurred within 24 hours of dialysis in 3 subjects. The lowest glucose recording for 14 subjects was within the first 24-hour period, with the majority being within 12 hours of dialysis. Thus, the results of our study suggest that type 2 diabetic maintenance HD patients, who are already at very high risk of CV morbidity and mortality, may be at increased risk of hypoglycaemia in the 24 hour period following a dialysis session. Current renal practice includes assessment of glycaemic control by blood glucose measurement while the patient is on haemodialysis. However, physicians caring for these patients need to be aware of this phenomenon and consider enhanced monitoring for these patients who may develop hypoglycaemia several hours after they have left the dialysis unit.

The subjects in this study were typical of the UK type 2 diabetes HD population with a long duration of diabetes (18.8 ±7.6 yrs) and high prevalence rates of established vascular disease (15/17). Our preliminary study suggests that CGM offers clinically useful data for such a high risk group. Larger studies on HD populations will be required to determine if data from CGM should be used for medication adjustments around dialysis days in order to optimise glycaemic control and avoid hypoglycaemia.

As glycaemic targets become redefined to avoid over aggressive management in high CVD risk individuals it is important that the measurements of glycaemic control in HD patients are as informative as possible.

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REFERENCES:
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Table 1. Clinical details of 17 subjects whose CGM data was included in the final analysis. Abbreviations used: CVD, documented history of vascular disease defined as ischaemic heart disease (history of MI, revascularisation procedure or angiographically proven coronary disease), cerebrovascular disease (history of CVA or TIA) or peripheral vascular disease (history of amputation due to gangrene, revascularisation procedure or angiographically/Doppler proven peripheral vascular disease).
Figure 1. CGM data for day on (Day 1) and day off dialysis (Day 2), expressed as area under curve (AUC) glucose (A) and mean glucose (B) for each 24 hour period. Data for individual subjects are represented as triangles connected by lines. The mean ± SD for each 24 hour period is represented as a square. A. Mean ± SD area under the 3 minute glucose curve for the whole study group was 5932.1 ± 2673.6 on the day off dialysis vs. 4694 ± 1988 mmol.3min.L⁻¹ on the day on dialysis, p=0.022. B. Mean ± SD CGM glucose values for the whole group were 12.6 ± 5.6mmol.L⁻¹ on the day off dialysis vs. 9.8 ± 3.8 mmol.L⁻¹ on the day on dialysis, p=0.013.

Figure 2. Nocturnal CGM data for the 6 hour period from midnight to 6 am for day on (Night 1) and day off dialysis (Night 2) expressed as area under curve (AUC) glucose (A) and mean glucose (B). Data for individual subjects are represented as triangles connected by lines. The mean ± SD for each 24 hour period is represented as a square. A. Mean ± SD area under the 3 minute glucose curve for the whole study group was 1541 ± 834 for the night of the day off dialysis (night 2) vs. 1137 ± 529 mmol.3min.L⁻¹ for the night of the day on dialysis (night 1), p<0.05. B. Mean ± SD CGM glucose values for the whole group were 12.9 ± 7.0mmol.L⁻¹ on night 2 vs. 9.5 ± 4.4 mmol.L⁻¹ on night 1.
CGM assessment in dialysis

A

AUC (mmol.3.min.L⁻¹)

Day 1  Day 2

B

Mean glucose (mmol.L⁻¹)

Day 1  Day 2
CGM assessment in dialysis

A

![Graph A](image)

AUC (mmol/L min L⁻¹)

Night 1 Night 2

B

![Graph B](image)

Mean glucose (mmol/L⁻¹)

Night 1 Night 2