Day-to-day variation of insulin requirements of patients with type 2 diabetes and end-stage renal disease undergoing maintenance hemodialysis

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Objective: To evaluate day-to-day variations of insulin needs in Type 2 diabetic patients with end-stage renal disease (ESRD) on maintenance hemodialysis (HD).

Research design and methods: We developed a 24-hour euglycemic clamp in patients receiving an average 2200 calories in a standardized 3-meal and 2-snack regimen per day adjusted to body size and sex. Intravenous insulin was adjusted every 30 minutes to achieve 5.5±1.1mmol/l glycemia over 24 hours pre-HD, during HD session, and 24 hours post-HD in 10 type 2 diabetic patients aged 55.7±8.7 years with 11.9±4.5 years diabetes duration, undergoing maintenance HD since 2.3±2.3 years. Insulin requirements were derived from the dose of insulin administered to maintain euglycemia per period of time, and day-to-day comparisons performed.

Results: Mean capillary glycemia was 5.5±0.3mmol/l pre-HD and 5.3±0.2mmol/l post-HD (p=0.39). Pre- and post-HD area under the glucose curve were comparable. This was achieved by infusing 23.6±7.7IU/24h pre-HD vs. 19.9±4.9IU/24h post-HD, indicating 15.3%-decrease post HD (p=0.09). Basal insulin needs decreased from 0.4±0.1/hour pre-HD to 0.3±0.1/hour post-HD (p=0.01). Total boluses were decreased by 2.2±3.1IU (p=0.15). Changes in blood urea did not correlate with changes in insulin needs (r=0.1, p=0.79).

Conclusions: The present study has demonstrated a significant 25% reduction in basal insulin requirements the day after dialysis compared to the day before. No significant change in boluses was observed, and overall the reduction of total insulin requirements was -15% equivalent to -4IU/day post HD of marginal statistical significance.
Diabetes mellitus is the most common cause of end-stage renal disease (ESRD), affecting at least one third of patients starting chronic dialysis worldwide (1). Insulin resistance is a characteristic feature of type 2 diabetes, and also of patients with chronic uremia (2-4). Insulin resistance and reduced clearance of insulin are factors that would lead to swings in glycemic levels, making tight glycemic control a daunting task in diabetic patients in end-stage renal disease. In addition, hemodialysis improves insulin sensitivity and also insulin clearance, making it more difficult to determine insulin requirements for patients with ESRD undergoing maintenance hemodialysis (HD), and therefore exposing them to acute metabolic incidents (5, 6). It is uncertain whether dialysis has a potential effect on pre to post dialysis days exogenous insulin requirements. Indeed, there is currently no evidence base recommendation for the adjustment of insulin dose post hemodialysis in diabetic patients. This study was undertaken to determine the insulin requirements necessary to achieve euglycemia over 24 hours pre-hemodialysis, during hemodialysis and 24 hours post-hemodialysis in type 2 diabetic patients with chronic kidney disease on maintenance hemodialysis.

METHODS
Patients were eligible to participate if they had a confirmed diagnosis of type 2 diabetes and stage 5 chronic kidney disease, and had given written informed consent to participate, and had been undergoing maintenance hemodialysis for at least 3 months. Patients with type 1 diabetes, those who had current acute illness or less than 10 days from the initial visit, patients taking drug that can modify glucose metabolism excluding insulin and other oral anti-diabetics, and those with pregnancy were not eligible.

Procedure: The study procedure involved an inclusion visit, and an exploration comprising one pre-hemodialysis, one per-hemodialysis, and one post-hemodialysis phase.

Inclusion visit: Within one week following an information visit, patients signed informed-consent form and were assessed for eligibility. Of the 12 eligible patients who were invited, 2 refused to participate because of lack of time. The exploration took place after adjustments of treatment in order to achieve near normoglycemic control at least 3 days prior to exploration.

Exploration: Participants were invited to arrive the hospital at least 24 hours before their index hemodialysis session. The exploration started after an overnight fast of at least 8 hours, and 24 hours before the index dialysis session. Patients were admitted for 50-52 consecutive hours in three continuous phases (pre, per and post-HD) and took place at the Endocrinology and the Hemodialysis units. During these explorations, a standardized meal plan comprising 2200 ± 200 calories (35cal/kg) with 55 ± 5% of carbohydrate daily was provided to the patients, distributed in 3 meals and 2 snacks per day adjusted to body size and sex. Meals were prepared by the same person for all subjects and were identical in type, composition, recipe and cooking method.

Pre-hemodialysis phase: The pre-hemodialysis phase started after an 8-h overnight fast with initial anthropometric measurements and resting electrocardiogram, and lasted at least 23 hours. Insulin was administered continuously using an electric syringe pump, and capillary blood glucose, insulin flow rate and the presence of any signs of hypoglycemia were monitored every one hour, and every thirty minutes until 2 hours postprandial.

Hemodialysis phase: Insulin infusion continued without interruption during the hemodialysis session. It lasted for 4 hours with the following systematically recorded at
the beginning and at the end of hemodialysis session: time, blood pressure and pulse rate, weight, body composition. Capillary blood glucose and the insulin flow rate were recorded every thirty minutes. Five milliliters of venous blood was collected for the measurement of blood urea nitrogen and serum creatinine immediately before and after the session.

Post-hemodialysis phase: This phase lasted at least 23 hours from the end of the hemodialysis session with follow up and intervention identical to the pre-hemodialysis phase. A final visit was organized to confirm the absence of study-related adverse event one week after discharge from hospital.

Measurements: Blood pressure was measured in mmHg after 5 minutes of rest, in the sitting position using an electronic sphygmomanometer (Omron M5I). Weight to the nearest 0.1kg and body composition were measured by impedancemetry and expressed as percent body fat, body water and lean body mass (Tanita BC 418MA, Tokyo, Japan). Height was measured to the nearest 0.5cm in the erect position using a wall stadiometer. Body mass index (BMI) was calculated as weight/height² in kg/m². Waist circumference was measured to the nearest cm at mid level between iliac crest and lowest rib during expiration.

Insulin requirements: The 24-hour euglycemic clamp. The insulin requirements were determined by maintaining euglycemia by adjusting insulin infusion rate to measured capillary glucose using a 24-hour euglycemic clamp in near free-living conditions. Briefly, we aimed to keep the blood glucose at 5.5 ± 1.1mmol/L throughout the exploration. The insulin infusion was set at a basal insulin flow rate of 0.3IU/h, and a bolus dose of 3IU of insulin was started 5 minutes before each meal. Capillary blood glucose was measured just before every meal, then every 30 minutes for 2 hours in postprandial period, then every 1 hour during the rest of the day and night using Hemocue® Glucose 201 RT analyzer. The insulin flow rate was adjusted accordingly.

Blood urea nitrogen and serum creatinine were determined on venous blood samples collected immediately before, and at the end of the HD session using colorimetric methods. The quality of dialysis was calculated as the logarithm of the ratio of serum urea concentrations at the beginning and at the end of hemodialysis.

Adverse events. Expected adverse events were hypoglycemia and local reaction at the site of infusion and were monitored for as well as non predictable events.

Ethics. The study was approved by the National Ethical Committee of Cameroon.

Statistical analysis: The statistical analysis was done using SPSS for Windows software version 15.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± standard deviation unless otherwise specified. Area under the curve was calculated using the trapezoidal formula. Comparisons between parameters were performed by paired t test. Spearman correlation was used where necessary.

RESULTS

Study population. This study was carried out on 10 patients undergoing two to three times weekly maintenance hemodialysis aged 55.7 ± 8.7 years (range 46.0 - 74.0 years) with 11.9 ± 4.5 years known duration of diabetes, 2.3 ± 2.3 years duration of maintenance hemodialysis, 22.7 ± 4.5 kg/m² mean BMI, and 88.3 ± 7.3 cm mean waist circumference. Their mean total hemoglobin level was 10.2 ± 1.5g/dL and HbA1c was 8.0 ± 1.2%.

Hemodialysis. Hemodialysis induced a decrement in circulating blood urea nitrogen of -69.3 ± 15.5% (3.7 ± 1.7 before versus 0.9 ± 0.4 g/L after, p = 0.0009), and -61.6 ± 33.4 mg/L of serum creatinine [85.6 ± 36.6mg/l versus 24.9 ± 9.5mg/l, p = 0.0002]. Estimated
body water decreased from 39.1 ± 5.2 L to 34.7 ± 4.2 L after hemodialysis (p = 0.0003).

**Blood glucose variations.** Over the 52 hours of investigation, participants had an average of 64 ± 2 determinations of capillary glycemia each, with a mean value of 5.3 ± 0.8 mmol/L. The lowest blood glucose levels recorded was 3.2 mmol/L pre-HD, 3.9 mmol/L per-HD, and 3.7 mmol/L post-HD. All were asymptomatic. Overall euglycemia was achieved throughout the investigation with the area under the glucose curve pre and post HD that were comparable (122.2mmol pre HD versus 121.8mmol post HD, NS).

**Insulin requirements:** Total insulin requirements and circadian variations: On average, the 24-hour total dose of insulin needed to achieve euglycemia was 23.6 ± 7.7 IU pre HD versus 19.9 ± 4.9 IU post HD (p = 0.09). The circadian distribution of the insulin requirements pre-HD was 28.0% from 6.00-12.00 hours, 28.8% from 12.00-18.00 hours, 29.7% from 18.00-24.00 hours, and 13.5% from 24.00-06.00 hours as shown in table 1. The decrease in total insulin requirements was more marked for the 12.00-18.00 hours period (Table 1).

**Basal and bolus insulin:** Basal insulin rate decreased by 25% post-HD (-0.1 IU/hour) compared to pre-HD while boluses did not change significantly as shown in table 2.

**Correlation with urea:** There was no correlation between change in urea and change in insulin requirements (Rs, = 0.10, P = 0.78).

**CONCLUSIONS**

Using a 24-hour euglycemic clamp in near free living conditions, this study has demonstrated a 15% decrease in the daily insulin needs on the day after hemodialysis compared to the daily insulin needs before hemodialysis, with a significant reduction of basal hourly insulin requirements by 25%, unchanged boluses, and unchanged body weight-indexed total insulin dose in a group of type 2 diabetic patients on maintenance hemodialysis.

The limited sample size is likely to explain the marginal statistical significance of the difference in total insulin dose variations. Despite this limitation, because basal insulin requirements were markedly and consistently reduced post hemodialysis, the difference appeared clinically and statistically significant. The use of intravenous route for insulin administration in this investigation deserve some caution for the generalization to clinical situations were subcutaneous route is used, and validation in type 1 diabetic patients would also be required. Because each patient was his own control, and because calorie intake and dialysis procedure were standardized, the influence of possible confounding determinants of insulin requirements was minimized.

Although the importance of intensive blood glucose control on the progression of renal disease has been demonstrated in both type 1 (7) and type 2 diabetes (8), it is still unclear whether such an approach would significantly influence morbidity and mortality in patients with end stage renal disease (9-12). Nevertheless, there is significant published evidence to indicate that such patients are at high risk of life-threatening glucose excursions and that the management is cumbersome (9-12). However, ADA clinical practice recommendations do not currently address the adjustment of insulin therapy in diabetic patients with chronic kidney disease undergoing hemodialysis (13).

It is expected that hemodialysis, mainly by clearing circulating urea would improve insulin sensitivity both on an acute and chronic basis (14). In fact, DeFronzo et al, have shown that after 10 weeks of thrice weekly hemodialysis there is an improvement in insulin sensitivity in uremic patients (15). In our study, although we did not observe a significant correlation between the change in insulin requirements and change in urea we
cannot exclude the pathophysiological relation between improvement of insulin sensitivity and the removal of blood urea nitrogen as previously reported (14,16). Although insulin is poorly dialyzed, greater insulin clearance on the dialysis day may also influence the effectiveness of insulin on the post-dialysis day. The insulin requirements indexed to body weight did not change significantly, suggesting that HD-induced body weight changes are part of the mechanism.

In conclusion, we have shown in a population with an average 2 years of maintenance hemodialysis that on the day after hemodialysis there is a significant 25% decrease in basal insulin requirements of diabetic patients with ESRD the day post-HD compared to the day pre-HD for comparable food consumption, but no significant change in bolus pre-meal insulin. These results therefore support a systematic reduction of basal exogenous insulin administration by 25% in type 2 diabetic patients undergoing hemodialysis the day after dialysis.

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**Conflict of interest:** none
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Table 1. Circadian variation of insulin requirements in the participants.

| Time Period             | Before Dialysis | After Dialysis | P (t-test)* |
|-------------------------|-----------------|----------------|-------------|
| 06:00 to 12:00h         | 6.61 ± 2.45     | 5.87 ± 1.29    | 0.30        |
| 12:00 to 18:00h         | 6.82 ± 2.47     | 5.19 ± 1.98    | 0.048       |
| 18:00 to 24:00h         | 6.98 ± 2.71     | 6.41 ± 1.43    | 0.43        |
| 24:00 to 06:00h         | 3.18 ± 1.57     | 2.49 ± 1.25    | 0.22        |

* day after versus day before dialysis by paired t-test.

Table 2. Insulin requirements on pre – and post-hemodialysis days in study participants

| N | Number of hours of investigation (h) | Number of bolus administered (n) | Total bolus insulin (IU) | Basal insulin flow rate (IU/H) | Total dose of insulin administered (IU) | Total dose of insulin (IU/kg/day) | Calorie intake (cal) |
|---|--------------------------------------|----------------------------------|--------------------------|---------------------------------|----------------------------------------|---------------------------------|---------------------|
|   | 10                                   | 10                               | 23.8 ± 0.5               | 4.8 ± 2.2                       | 11.8 ± 4.8                             | 0.4 ± 0.2                      | 2304 ± 400          |
|   |                                      |                                  | 23.6 ± 0.6               | 3.4 ± 0.7                       | 9.6 ± 1.7                              | 0.3 ± 0.1                      | 2167 ± 376          |
| P*|                                      |                                  |                          |                                 |                                        |                                 |                     |
|   |                                      |                                  |                          |                                 |                                        |                                 |                     |

*day after dialysis value versus day before dialysis by paired t-test.