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.

RESEARCH DESIGN AND METHODS — We developed a 24-h euglycemic clamp in patients who received an average of 2,200 calories in a standardized three-meal and two-snack regimen per day, adjusted to body size and sex. Intravenous insulin was adjusted every 30 min to achieve 5.5 ± 1.1 mmol/l glycemia over 24 h prehemodialysis, during hemodialysis session, and 24 h posthemodialysis in 10 type 2 diabetic patients, aged 55.7 ± 8.7 years with 11.9 ± 4.5 years diabetes duration, undergoing maintenance hemodialysis for 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 ± 0.3 mmol/l prehemodialysis and 5.3 ± 0.2 mmol/l posthemodialysis ($P = 0.39$). Pre- and posthemodialysis areas under the glucose curve were comparable. This was achieved by infusing 23.6 ± 7.7 IU/24 h prehemodialysis vs. 19.9 ± 4.9 IU/24 h posthemodialysis, indicating a 15.3% decrease posthemodialysis ($P = 0.09$). Basal insulin needs decreased from 0.4 ± 0.1/h prehemodialysis to 0.3 ± 0.1/h posthemodialysis ($P = 0.01$). Total boluses were decreased by 2.2 ± 3.1 IU ($P = 0.15$). 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 with the day before. No significant change in boluses was observed, and overall the reduction of total insulin requirements was −15% equivalent to −4 IU/day posthemodialysis of marginal statistical significance.

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Diabetes 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 lead to swings in glycemic levels, making tight glycemic control a daunting task for diabetic patients with ESRD. 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 and therefore exposing them to acute metabolic incidents (5,6). It is uncertain whether dialysis has a potential effect on pre- to postdialysis days' changes in exogenous insulin requirements. Indeed, there is currently no evidence-based recommendation for the adjustment of insulin dose posthemodialysis in diabetic patients. This study was undertaken to determine the insulin requirements necessary to achieve euglycemia over 24 h prehemodialysis, during hemodialysis, and 24 h posthemodialysis in type 2 diabetic patients with chronic kidney disease on maintenance hemodialysis.

RESEARCH DESIGN AND METHODS

Patients were eligible to participate if they had a confirmed diagnosis of type 2 diabetes, had stage 5 chronic kidney disease, 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; those who were <10 days from the initial visit; those taking drugs that can modify glucose metabolism, excluding insulin and other oral antidiabetes drugs; and those who were pregnant were not eligible.

The study procedures involved an inclusion visit and an exploration comprising one prehemodialysis, one perhemodialysis, and one posthemodialysis phase.

Inclusion visit

Within 1 week following an information visit, patients signed informed consent forms and were assessed for eligibility. Of 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

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near-normoglycemic control at least 3 days prior to exploration.

Exploration

Participants were invited to arrive at the hospital at least 24 h before their index hemodialysis session. The exploration started after an overnight fast of at least 8 h and 24 h before the index dialysis session. Patients were admitted for 50–52 consecutive hours in three continuous phases (pre-, per-, and posthemodialysis) and took place at the endocrinology and the hemodialysis units. During these explorations, a standardized meal plan comprising 2,200 ± 200 calories (35 cal/kg) with 55 ± 5% carbohydrate daily was provided to the patients, distributed in three meals and two 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.

Prehemodialysis phase

The prehemodialysis phase started after an 8-h overnight fast with initial anthropometric measurements and resting electrocardiogram and lasted at least 23 h. 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 1 h and every 30 min until 2 h postprandial.

Hemodialysis phase

Insulin infusion continued without interruption during the hemodialysis session. It lasted for 4 h, with the following systematically recorded at the beginning and at the end of hemodialysis session: time, blood pressure and pulse rate, weight, and body composition. Capillary blood glucose and the insulin flow rate were recorded every 30 min. Five milliliters of venous blood were collected for the measurement of blood urea nitrogen and serum creatinine immediately before and after the session.

Posthemodialysis phase

This phase lasted at least 23 h from the end of the hemodialysis session, with follow-up and intervention identical to the prehemodialysis phase. A final visit was organized to confirm the absence of study-related adverse events 1 week after discharge from hospital.

Measurements

Blood pressure was measured (in mmHg) in the sitting position using an electronic sphygmomanometer (Omron M5I), after 5 min of rest. Weight to the nearest 0.1 kg and body composition were measured by impedancemetry and expressed as percent body fat, body water, and lean body mass (Tanita BC 418MA; Tanita, Tokyo, Japan). Height was measured to the nearest 0.5 cm in the erect position using a wall stadiometer. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference was measured to the nearest centimeter at mid-level between the iliac crest and lowest rib during expiration.

Insulin requirements

The 24-h euglycemic clamp. The insulin requirements were determined by maintaining euglycemia by adjusting insulin infusion rate to measured capillary glucose using a 24-h euglycemic clamp in near–free-living conditions. Briefly, we aimed to keep the blood glucose at 5.5 ± 1.1 mmol/l throughout the exploration. The insulin infusion was set at a basal insulin flow rate of 0.3 IU/h, and a bolus dose of 3 IU insulin was started 5 min before each meal. Capillary blood glucose was measured just before every meal then every 30 min for 2 h in the postprandial period then every 1 h during the rest of the day and night using a 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 hemodialysis 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, which were monitored for, as well as unpredictable 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, Chicago, IL). Results were expressed as means ± SD, 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) with known duration of diabetes 11.9 ± 4.5 years, duration of maintenance hemodialysis 2.3 ± 2.3 years, mean BMI 22.7 ± 4.5 kg/m^2, and mean waist circumference 88.3 ± 7.3 cm. Their mean total hemoglobin level was 10.2 ± 1.5 g/dl and A1C was 8.0 ± 1.2%.

Hemodialysis

Hemodialysis induced a decrement in circulating blood urea nitrogen of −69.3 ± 15.5% (3.7 ± 1.7 g/l before vs. 0.9 ± 0.4 g/l after, $P = 0.0009$) and −61.6 ± 33.4 mg/l serum creatinine (85.6 ± 36.6 mg/l vs. 24.9 ± 9.5 mg/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 52 h 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 prehemodialysis, 3.9 mmol/l perhemodialysis, and 3.7 mmol/l posthemodialysis. All were asymptomatic. Overall euglycemia was achieved throughout the investigation with the area under the glucose curve pre- and posthemodialysis that were comparable (122.2 mmol prehemodialysis vs. 121.8 mmol posthemodialysis, P = NS).

Insulin requirements

Total insulin requirements and circadian variations. On average, the 24-h total dose of insulin needed to achieve euglycemia was 23.6 ± 7.7 IU prehemodialysis vs. 19.9 ± 4.9 IU posthemodialysis ($P = 0.09$). The circadian distribution of the insulin requirements prehemodialysis was 28.0% from 0600 to 1200 h, 28.8% from 1200 to 1800 h, 29.7% from 1800 to 2400h, and 13.5% from 2400 to 0600 h as shown in Table 1. The decrease in total insulin requirements was more marked for the 1200- to 1800-h period (Table 1).

Table 1—*Circadian variation of insulin requirements in the participants*

	0600–1200 h	1200–1800 h	1800–2400 h	2400–0600 h
Before dialysis	6.61 ± 2.45	6.82 ± 2.47	6.98 ± 2.71	3.18 ± 1.57
After dialysis	5.87 ± 1.29	5.19 ± 1.98	6.41 ± 1.43	2.49 ± 1.25
P (*t* test)*	0.30	0.048	0.43	0.22

Data are means ± SD. *Day after vs. day before dialysis by paired *t* test.

Basal and bolus insulin

Basal insulin rate decreased by 25% posthemodialysis (−0.1 IU/h) compared with prehemodialysis, 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 ($R_s = 0.10$, $P = 0.78$).

CONCLUSIONS— Using a 24-h 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 with 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 posthemodialysis, the difference appeared clinically and statistically significant. The use of the intravenous route for insulin administration in this investigation deserves some caution for the generalization to clinical situations where subcutaneous route is used. Validation in type 1 diabetic patients would also be required. Because each patient was his or her 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 (8) diabetes, it is still unclear whether such an approach would significantly influence morbidity and mortality in patients with ESRD (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, American Diabetes Association 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 on both an acute and chronic basis (14). In fact, DeFronzo et al. (15) have shown that after 10 weeks of thrice-weekly hemodialysis there is an improvement in insulin sensitivity in uremic patients. 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 postdialysis day. The insulin requirements indexed to body weight did not change significantly, suggesting that hemodialysis-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 posthemodialysis compared with the day prehemodialysis for comparable food consumption, but no significant change in bolus premeal 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.

Table 2—*Insulin requirements on pre- and posthemodialysis days in study participants*

	Day before dialysis	Day after dialysis	*P**
n	10	10	
Number of hours of investigation (h)	23.8 ± 0.5	23.6 ± 0.6	0.47
Number of bolus administered (*n*)	4.8 ± 2.2	3.4 ± 0.7	0.04
Total bolus insulin (IU)	11.8 ± 4.8	9.6 ± 1.7	0.15
Basal insulin flow rate (IU/h)	0.4 ± 0.2	0.3 ± 0.1	0.01
Total dose of insulin administered (IU)	23.6 ± 7.7	19.9 ± 4.9	0.09
Total dose of insulin (IU/kg/day)	0.36 ± 0.12	0.32 ± 0.08	0.19
Calorie intake (cal)	2,304 ± 400	2,167 ± 376	0.44

Data are means ± SD. *Day after dialysis value vs. day before dialysis by paired *t* test.

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