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Bicarbonate dialysis compared to hemodiafiltration on glycemic excursions in patients with end-stage renal disease with and without type 2 diabetes mellitus

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ABSTRACT

Aim: To evaluate the effects on glycemic excursions during bicarbonate dialysis (BHD) compared to hemodiafiltration (HDF) in type 2 diabetic or not diabetic patients affected by end-stage renal disease (ESRD).
Material and Methods: Thirty-six patients (20 affected by type 2 diabetes mellitus, and 16 not diabetic patients) were evaluated and underwent BHD dialysis, followed by HDF dialysis two days later. All patients underwent also glucose continuous monitoring system, using *i*Pro Continuous Glucose Monitor System (Medtronic MiniMed) starting just before the BHD, and ending five days later, two days after the HDF dialysis. Glycemic control was estimated as the mean blood glucose (MBG), the area under the glucose curve above 70 mg/dl ($AUC_{>70}$) or 180 mg/dl ($AUC_{>180}$), and the percentage of time above 70 mg/dl ($t_{>70}$) or 180 mg/dl ($t_{>180}$). Intraday glycemic variability was assessed as the standard deviation (SD), M value, and the mean amplitude of glycemic excursions (MAGE). Day-to-day glycemic variability was assessed as the mean of daily difference (MODD), that is the mean of the absolute difference among glucose values taken on 2 consecutive days at the same time.
Results: glycemic control was better with HDF: MBG, and $AUC_{>180}$ were lower during HDF compared do BHD. We also observed a significant decrease of glycemic excursions during HDF dialysis: SD, M value, and the MAGE value were lower with HDF. The MODD value was significantly changed in BHD group, while no differences were recorded during HDF.
Conclusion: HDF seems to greater reduce glycemic excursions during the treatment compared to BHD.

1. Introduction

According to the latest data, a conspicuous increase in the prevalence of diabetic patients undergoing dialysis was observed in Italy (from 6% in 1993 to 12.15% in 2008) (Panzetta et al., 2008). Type 2 diabetes mellitus is characterized by sustained chronic hyperglycemia and increased amplitude of glycemic excursions. It is well known that glycemic control closely correlates with morbidity and mortality in diabetic end-stage renal disease (ESRD) patients on dialysis; poor glycemic control is associated with increased morbidity from vascular and diabetic complications, malnutrition, and shortened survival in diabetics on chronic dialysis (Jin et al., 2015; Jun et al., 2015; Osonoi et al., 2014). On the other hand, there are many reasons to think that both upward and downward acute fluctuations of glucose around a mean value activate the oxidative stress (Monnier & Colette, 2008). There has been much debate about the need of treating not adequate glycemic control and increased glycemic variability in patients with type 2 diabetes. What is certain, however, is that glycemia should be monitored by frequent and careful glucose determinations in patients with ESRD, especially those with diabetes. Maintenance dialysis patients, with or without diabetes, in fact, may experience both hyper- and hypoglycemia through multi-factorial mechanisms relating to kidney dysfunction, the uremic environment, and dialysis (Rhee et al., 2014). Moreover, exogenous insulin and hypoglycemic agents pharmacokinetic are also altered by ESRD and hemodialysis, with different profiles according to the dialysis pattern (Haviv,

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Sharkia, & Safadi, 2000). Previous studies suggested that classical markers of glycemic control, such as glycated hemoglobin (HbA_{1c}) may be misleading in patients with ESRD due to analytical interferences, shortened half-life of red blood cells and abnormal albumin levels (Lee, Szeto, & Benzie, 2002). To by-pass this problem, new techniques have been proposed to monitor glycemic variability; at this regards, continuous glucose monitoring system (CGMS) proved to be reliable compared to self blood glucose monitoring system in a sample of healthy free-living subjects to assess glucose excursions (Derosa et al., 2009). Further studies suggests that the use of iterative CGMS sequences in a population of patients with diabetes on chronic dialysis treatment may result in more treatment adaptation and thus, in an improvement of glucose control without increased hypoglycemic risk (Joubert et al., 2015).

On this basis, we decided to conduct a study to compare the glycemic excursions in patients affected by ESRD undergoing two different dialytic methods, bicarbonate dialysis (BHD) and hemodiafiltration (HDF) to understand which procedure is to prefer.

In order to better understand the effects of different dialysis techniques on glycemic variability, we chose to enroll both patients with type 2 diabetes mellitus, and patients without diabetes, who are expected to have minor or less variation in their blood glucose levels.

2. Material and methods

2.1. Study design

This case control study was conducted at the Department of Internal Medicine and Therapeutics, Fondazione IRCCS Policlinico S. Matteo, University of Pavia, Pavia, Italy, and at the Unit of Nephrology, Dialysis and Transplantation, Fondazione IRCCS Policlinico S. Matteo, University of Pavia, Pavia, Italy.

The study protocol was conducted in accordance with the Declaration of Helsinki and its amendments, and the Good Clinical Practice Guidelines. It was approved by the local Ethical Committee and all patients provided written informed prior to entering the study. TRIAL REGISTRATION: ClinicalTrials.gov NCT01049152.

All patients underwent two dialysis techniques, BHD and HDF, starting with BHD. Two days later, patients underwent HDF dialysis.

3. Patients

We enrolled 36 subjects, of both sex, aged ≥18, 16 with a condition of euglycemia, and 20 affected by type 2 diabetes mellitus according to the ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines criteria (Rydén et al., 2007). The mean age was 62.2 ± 9.4 years. Subjects' characteristics are presented in Table 1. All patients were affected by ESRD [defined by glomerular filtrate rate (GFR) <15 ml/min/1.73 m^2] requiring dialysis to survive and were receiving regular dialysis treatment with non-reused dialyzers 4 hours thrice weekly for at least 6 months. Among 20 type 2 diabetic patients, 9 were taking insulin and 11 were on dietetic therapy. No oral anti-diabetic treatment was used due to the end stage renal disease.

Subjects were excluded if they presented pathologies that could affect glucose metabolism (with the exception of type 2 diabetes mellitus) such as Cushing's syndrome, or alteration of thyroid function or if they were in treatment with drugs such as corticosteroids or non-steroidal anti-inflammatory drugs.

Subjects with infective or acute or chronic inflammatory disorders, or patients underwent organ transplantation were also excluded. Furthermore, patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, or neuropathy; impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex), or severe anemia. Patients with serious cardiovascular disease (CVD) (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions (as indicated by a history of ischemic stroke or a history of carotid revascularization) within 6 months before study enrollment also were excluded. Other reasons for exclusion included malignancy, malnutrition, vasculopathy, and malfunction of vascular access.

Suitable patients, identified from review of case notes and/or computerized clinic registries, were contacted by the investigators in person or by telephone.

Table 1
Anthropometric parameters of patients at baseline.

Parameters	
N	36
Sex (M/F)	20/16
Diabetes mellitus (M/F)	12/8
Age (years)	62.2 ± 9.4
Weight (Kg)	79.5 ± 12.8
Height (m)	1.69 ± 0.08
BMI (kg/m^2)	27.8 ± 3.5
Waist Cir. (cm)	94.7 ± 15.9
Abd. Cir. (cm)	101.2 ± 17.5
Hip Cir. (cm)	103.1 ± 13.2
HbA_{1c} (%)	7.1 ± 2.2
FPG (mg/dl)	139 ± 50
FPI (μU/ml)	19.6 ± 7.2
HOMA index	6.5 ± 5.1
TC (mg/dl)	194.2 ± 22.5
LDL-C (mg/dl)	132.3 ± 18.2
HDL-C (mg/dl)	43.8 ± 9.1
Tg (mg/dl)	90.3 ± 54.7

Data are expressed as mean ± standard deviation (SD).
BMI: body mass index; Abd. Cir.: abdominal circumference; Waist Cir.: waist circumference; Hip Cir.: hip circumference; FPG: fasting plasma glucose; FPI: fasting plasma insulin; HOMA index: homeostatic model assessment of insulin resistance; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides.

3.1. Assessments

All patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, and a 12-lead electrocardiogram. We also evaluated at baseline, HbA_{1c}, fasting plasma glucose, fasting plasma insulin, HOMA index, and lipid profile.

All plasmatic parameters were determined after a 12-h overnight fast. Venous blood samples were taken for all patients between 08.00 and 09.00. We used plasma obtained by addition of Na_2-EDTA, 1 mg/ml, and centrifuged at 3000 g for 15 minutes at 4 °C. Immediately after centrifugation, the plasma samples were frozen and stored at −80 °C for no more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in meters.

Capillary glycemia, necessary to calibrate the sensor, was evaluated using blood glucometer provided to the subjects at the study start (One Touch Verio® Blood Glucose Monitoring System).

Glycated hemoglobin level was measured by a high performance liquid chromatography (HPLC) method (DIAMAT, Bio-Rad, USA; normal values 4.2–6.2%), with intra- and interassay coefficients of variation (CsV) of <2% (Bunn, Gabbay, & Gallop, 1978).

Plasma glucose was assayed by glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay CsV of <2% (European Diabetes Policy Group, 1999).

Plasma insulin was assayed with Phadiaseph Insulin radio immunoassay (RIA) (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay CsV 4.6 and 7.3%, respectively) (Heding, 1972).