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Metabolic effects of dialyzate glucose in chronic hemodialysis: results from a prospective, randomized crossover trial

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Abstract

Background. There is no agreement concerning dialyzate glucose concentration in hemodialysis (HD) and 100 and 200 mg/dL (G100 and G200) are frequently used. G200 may result in diffusive glucose flux into the patient, with consequent hyperglycemia and hyperinsulinism, and electrolyte alterations, in particular potassium (K) and phosphorus (P). This trial compared metabolic effects of G100 versus G200.

Methods. Chronic HD patients participated in this randomized, single masked, controlled crossover trial (www.clinicaltrials.gov: #NCT00618033) consisting of two consecutive 3-week segments with G100 and G200, respectively. Intradialytic serum glucose (SG) and insulin concentrations (SI) were measured at 0, 30, 60, 120, 180, 240 min and immediately post-HD; P and K were measured at 0, 120, 180 min and post-HD. Hypoglycemia was defined as an SG <70 mg/dL. Mean SG and SI were computed as area under the curve divided by treatment time.

Results. Fourteen diabetic and 15 non-diabetic subjects were studied. SG was significantly higher with G200 as compared to G100, both in diabetic {G200: 192.8 ± 48.1 mg/dL; G100: 154.0 ± 27.3 mg/dL; difference 38.8 [95% confidence interval (CI): 21.2–56.4] mg/dL; $P < 0.001$} and non-diabetic subjects [G200: 127.0 ± 11.2 mg/dL; G100 106.5 ± 10.8 mg/dL; difference 20.6 (95% CI: 15.3–25.9) mg/dL; $P < 0.001$]. SI was significantly higher with G200 in non-diabetic subjects. Frequency of hypoglycemia, P and K serum levels, interdialytic weight gain and adverse intradialytic events did not differ significantly between G100 and G200.

Conclusion. G200 may exert unfavorable metabolic effects in chronic HD patients, in particular hyperglycemia and hyperinsulinism, the latter in non-diabetic subjects.

Keywords: diabetes mellitus; dialyzate; glucose; hemodialysis; insulin

Introduction

Hemodialysis (HD) fluid can be considered a temporary extension of the patient's extracellular fluid because of the bi-directional transport processes when blood and dialyzate are flowing through the dialyzer. Therefore, the composition of the dialyzate is critical for the patient's electrolyte and metabolic homeostasis. Glucose is a main dialyzate component, but there exists no general agreement on the optimal level. In the 1960s, prior to the general use of ultrafiltration in dialysis machines, the osmotic forces induced by glucose were used for fluid removal and dialyzate glucose concentrations of up to 1600 mg/dL were used for this reason [1]. After ultrafiltration, which has been firstly incorporated in a dialysis machine by the Swedish scientist Nils Alwall, became a standard feature of dialysis machines, high dialyzate glucose concentrations lost importance. The addition of dialyzate glucose remained standard of most dialysis providers, due to concerns about hypoglycemia, but the optimal dialyzate glucose concentration remained controversial. In the USA, a dialyzate glucose concentration of 200 mg/dL (11 mmol/L; G200) became standard until recently. In Europe, the most frequently used glucose concentration is 100 mg/dL (5.5 mmol/L; G100), whereas in some countries glucose-free dialyzate (G0) is used, mainly due to concerns about bacterial and fungal contamination and economic considerations.

While several studies on G0 versus G200 and G100, respectively [1–6], have been reported, data comparing G100 and G200 are scarce [1, 6]. In particular, G100 and G200 have never been compared in a randomized controlled trial (RCT).

Additionally, not much information has been reported in recent years on glucose kinetics during HD. There is evidence that glucose-containing dialyzate to some degree prevents glucose losses from the patient and thus reduces the risk of intradialytic hypoglycemia [2, 7, 8]. Diabetic

HD patients treated with oral anti-diabetic agents or insulin may be particularly prone to hypoglycemia because eating during HD is discouraged due to adverse effects on hemodynamic stability [9]. On the other hand, G200 may result in overt intradialytic hyperglycemia and transient hyperinsulinism [1, 2, 10].

Since insulin affects serum potassium levels by promoting cellular potassium (K) uptake, hyperinsulinism may thus reduce K removal by HD [10]. Hyperinsulinism may also reduce phosphorus (P) removal during HD due to increased cellular P uptake [11].

An additional theoretical consideration is the contribution of plasma glucose to plasma osmolality, although this effect may be deemed negligible [5]. However, it cannot be entirely excluded that intradialytic hyperglycemia may result in increased thirst after dialysis and higher interdialytic weight gains (IDWG); on the other hand, hyperglycemia may promote fluid shifts from the intracellular to the extracellular compartment and thus stabilizes blood pressure during ultrafiltration.

In order to address the questions outlined above, we embarked on an RCT of G100 and G200 in chronic HD patients. The primary endpoint was mean intradialytic serum glucose level; secondary endpoints included adverse intradialytic events such as hypoglycemia or other events requiring intervention as per the unit's policy, insulin levels, intradialytic glucose removal or gain, intradialytic K and P concentrations, systolic blood pressure (SBP), occurrence of cardiac arrhythmias and IDWG.

Materials and methods

Patient selection

Maintenance HD patients dialyzed thrice weekly on a regular schedule at two dialysis centers of the Renal Research Institute in New York City were included in this single-masked crossover RCT (www.clinicaltrials.gov: #NCT00618033). The study protocol was approved by the Institutional Review Board of Beth Israel Medical Center, New York City, NY. Patients signed informed consent prior to enrollment and the study was conducted in full accordance with the Declaration of Helsinki.

Patients were enrolled according to the inclusion and exclusion criteria (see below) regardless of gender, race and ethnicity. Inclusion criteria were age $\geq$18 years and HD vintage $>$30 days. Patients receiving HD other than thrice weekly, those with a history of infection, antibiotic treatment or hospitalization during the preceding month were excluded. The enrollment target was 15 diabetic and 15 non-diabetic patients.

Diabetes mellitus was defined by either anti-diabetic therapy (oral drugs or insulin) or a random blood glucose $>$200 mg/dL in the preceding 12 months.

Study design

The study comprised two randomized consecutive 3-week treatment periods (nine HD treatments during each period) with G100 and G200, respectively (Figure 1). Randomization of the treatment sequence was done at the facility level to avoid potential influence of facility practice patterns. Study coordinators assured proper delivery of the allocated treatment regimen. Throughout the entire study, patients were masked to dialyzate glucose levels. Blinding of study coordinators, technicians, nurses and physicians was not feasible for safety reasons. In order to maintain the single-masked design, dialyzate was administered via unlabled taps or jugs, depending on the facility. Dialyzer type (Fresenius Optiflux F180NR), treatment time, blood and dialyzate flow rates, target weights and medications remained unchanged throughout the entire 6-week study period. No food was provided during the study treatments and subjects were asked to refrain from eating.

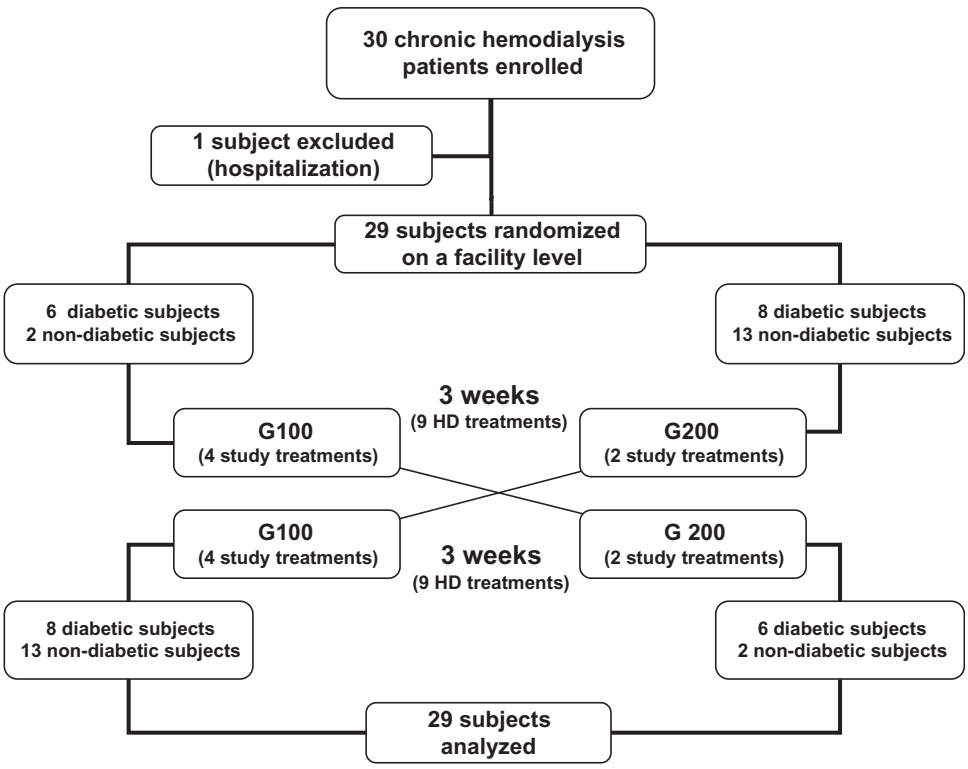

Fig. 1. Study flowchart.

Measurements

In the units enrolled in the study, no previous experience with G100 existed and G200 was the standard dialyzate. Therefore, in order to address concerns about the safety of G100, twice as many study treatments with G100 were scheduled (four with G100 and two with G100). Study treatments where blood samples were obtained were scheduled after long and short interdialytic intervals in a 1:1 ratio.

Biochemistry

Serum glucose and insulin levels were measured at 0, 30, 60, 120, 180 min and at the end of HD. Serum potassium and phosphorus were measured at 0, 120 min and at the end of HD. Glucose, phosphorus and potassium were measured with standard methods using the Olympus AU5400 analyzer (Olympus Diagnostics Systems, Center Valley, PA). Insulin was measured with a chemiluminescent immunoassay implemented on the Advia Centaur (Siemens Healthcare Diagnostics, Deerfield, IL). Hematocrit was estimated from clinical routine measurements of mean erythrocyte cell volume and red blood cell count. All measurements were performed at a certified laboratory (Spectra Laboratories; Rockleigh, NJ). Data of serum glucose are reported in conventional units (mg/dL), for conversion to SI units (mmol/L), values have to be multiplied by 0.0555.

Glucose kinetics. Mean intradialytic serum glucose and insulin concentrations (SG_{mean}; SI_{mean}) were calculated by the respective areas under the curves divided by the duration of the treatment in minutes. The area under the curve was calculated employing a third-order polynomial fit of all measured intradialytic serum glucose and insulin concentrations, respectively.

The glucose KoA of the dialyzer for the Fresenius Optiflux F180NR was determined to be 0.749 L/min as per *in vitro* experiments using aqueous solutions and heparinized bovine blood (D. Schneditz, unpublished data). Glucose clearance was calculated as [12]:

$$K = \frac{Q_p.Q_d.(1-f)}{Q_p - Q_d.f}, \quad (1)$$

where Q_p is the effective plasma flow in liters per minute, Q_d the dialyzate flow in liters per minute and

$$f = e^{KoA.\left(\frac{1}{Q_p}-\frac{1}{Q_d}\right)}. \quad (2)$$

The plasma flow (Q_p) in liters per minute was calculated as:

$$Q_p = Q_b.\left(1 - \frac{Hct}{100}\right), \quad (3)$$

where Q_b is the average blood flow during the treatment in liters per minute and Hct the hematocrit as volume percentage of whole blood.

Per definition, glucose flux into the patient was considered as positive, and out of the patient as negative.

The diffusive glucose mass transfer [MT $(t)_{diffusive}$] in mg within the time interval between two consecutive blood draws was calculated as follows:

$$MT(t)_{diffusive} = \left[K \cdot \left(G_{dialysate} - SG(t)_{average}\right)\right] \cdot t, \quad (4)$$

where SG $(t)_{average}$ is the average plasma water glucose concentration in mg/L (plasma concentration corrected for plasma void volume by the factor 0.93) during the time interval of the duration t in minutes. A positive glucose mass transfer corresponds to a diffuse glucose transfer from the dialyzate to the patient. The total intradialytic diffusive glucose mass transfer, MT $(total)_{diffusive}$, in mg, was calculated as the sum of individual glucose transfers over all time intervals.

The convective glucose mass transfer in mg during the time interval between two consecutive blood draws was calculated as follows:

$$MT(t)_{convective} = -\left(UFV(t) \cdot SG(t)_{average}\right), \quad (5)$$

where UFV is the ultrafiltration volume removed, in liters, during the time interval t, in minutes. The total convective glucose loss, MT $(total)_{convective}$ in milligram, was calculated as the sum of the individual convective glucose losses over all time intervals.

The total intradialytic extracorporal glucose mass transfer was calculated as the sum of diffusive and convective mass transfer:

$$MT = MT(total)_{diffusive} + MT(total)_{convective}. \quad (6)$$

Insulin kinetics. Dialyzer insulin clearance was estimated from insulin's molecular weight: a linear equation was generated (least squares regression) describing solute clearance as a function of the logarithm of the solute's molecular weight. The data used to fit this regression were the *in vitro* clearances of urea, sodium, creatinine, phosphorus, vitamin B12 and lysozyme at a solute diffusion volume flow rate of 0.3 L/min and a dialyzate flow rate of 0.5 L/min (provided by the dialyzer manufacturer) and the logarithms of those solutes' molecular weights. Insulin clearance was estimated using this equation, based on its molecular weight. The insulin mass transfer area coefficient (KoA) was then calculated according to Michaels [12] after correction for plasma void volume using the factor 0.93.

Other measures. Intradialytic SBP was recorded at time points 0, 30, 60, 120, 180 min and end of HD by an oscillometric method.

Holter recordings were performed after the long interdialytic interval, once each with HD100 and HD200, commencing about 10 min before HD. Electrocardiograms (ECGs) were continuously recorded at a sampling rate of 250 Hz with a three-lead Holter device (clickholter, Cardioline; HealthFrontier Inc., Branchburg, NJ) for 24 h. The Holter recordings were analyzed by an ECG analyst blinded to the dialyzate.

In diabetic subjects, hypoglycemia was defined as a serum glucose <70 mg/dL [13].

Intradialytic adverse events and appropriate interventions (such as administration of saline in the event of intradialytic hypotension) were defined and treated as per the unit's policy.

IDWG was defined as the difference between pre-HD weight and the preceding post-HD weight.

Statistical analyses

Normality of data was assessed by the Kolmogorov–Smirnoff test. Student's *t*-test was employed to compare demographics, treatment characteristics, SBP, ultrafiltration volume, IDWG, mean glucose and insulin concentrations, diffusive and convective glucose mass transfer during HD using G100 and G200. *Z*-test was used to test the statistical significance of insulin and glucose transfer. Mann–Whitney *U*-test was used to compare the difference of occurrence of cardiac arrhythmias between G100 and G200. McNemar change test was employed to compare the incidence of hypoglycemia and adverse intradialytic events with G100 and G200 on a patient level. In two sensitivity analyses, (i) diabetic subjects not on antidiabetic medication or insulin and (ii) treatments where food was ingested in the very beginning of the HD treatment were excluded. A P-value <0.05 was considered statistically significant for all tests. All statistical analyses were done with SPSS 17.0 (SPSS Inc., Chicago, IL).

Results

Thirty patients (15 diabetic and 15 non-diabetic subjects) were enrolled during the period from April to June 2008. One subject had to be withdrawn prior to randomization due to hospitalization (Figure 1). Twenty-nine subjects underwent 551 study treatments in total, 286 with G200 and 264 with G100, respectively. Demographics are shown in Table 1 and dialysis treatment parameters in Table 2.

Biochemistry

Serum glucose (SG) and insulin (SI). SG_{mean} was significantly higher with G200 ($n = 56$) compared to G100 ($n = 104$) (Table 3) in diabetic (G100: 154.0 ± 27.3 mg/dL; G200: 192.8 ± 48.1 mg/dL; $P < 0.001$) and non-diabetic (G100: 106.5 ± 10.8 mg/dL; G200: 127.0 ± 16.8 mg/dL; $P < 0.001$) subjects. At the beginning of HD, SG did not differ between G100 and G200 in either group (Table 2). By 30 min, both diabetic and non-diabetic subjects showed

Table 1. Demographics of study cohort[a]

	All subjects	Diabetic subjects	Non-diabetic subjects
n	29	14	15
Age (years)	54 ± 13	59 ± 12	49 ± 11
Gender (m/f)	15/14	6/8	9/6
Race (black/non-black)	16/13	8/6	6/9
Dialysis vintage (years)	5 ± 4	3 ± 3	6 ± 5
Height (cm)	167 ± 10	164 ± 11	170 ± 10
Post-HD weight (kg)	81 ± 19	78 ± 19	84 ± 20
Post-HD body mass index (kg/m^2)	28 ± 7	28 ± 6	28 ± 7
Beta blocker (β_1-selective/α_1-β_1-selective)	6/8	3/5	3/3
Anti-hypertensive drugs (ACE inhibitors/ARB/CCB)	4/4/13	2/4/8	2/0/5
Type of diabetes (Type 1/Type 2)	1/13	1/13	n.a.
Diabetes-related medication (insulin/oral anti-diabetic drugs)	9/3	9/3	n.a.

[a]Data reported as mean ± SD. No statistically significant differences between G100 and G200 have been found. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; n.a., not applicable.

Table 2. HD treatment parameters[a]

	Diabetic subjects ($n = 14$)		Non-diabetic subjects ($n = 15$)	
	G100	G200	G100	G200
Treatments (number)	126	138	138	148
Treatment time (min)	207 ± 31	210 ± 33	213 ± 25	214 ± 21
Dialyzate Na^+ concentration (mmol/L)	138	138	138	138
Dialyzate K^+ concentration (mmol/L) (2/3)	13/1	13/1	14/1	14/1
Dialyzate Ca^{++} concentration (mmol/L) (1.125/1.5)	14/0	14/0	14/1	14/1
Dialyzate temperature (°C)	37	37	37	37
Blood flow (mL/min)[b]	401 ± 13	408 ± 28	396 ± 32	399 ± 21
Hematocrit (%)[b]	36 ± 4	35 ± 3	35 ± 3	36 ± 4
Plasma flow (mL/min)[b]	259 ± 21	265 ± 24	257 ± 23	256 ± 20
Urea kinetic volume (L)	34 ± 6	34 ± 6	36 ± 7	36 ± 7
IDWG (kg)	2.3 ± 0.9	2.3 ± 1.0	2.3 ± 1.3	2.4 ± 1.1
Weight change during HD (pre-HD weight – post-HD weight) (kg)	2.3 ± 1.0	2.3 ± 1.2	2.4 ± 0.8	2.9 ± 2.1
Intradialytic saline administration (count)	21	24	25	26
Reasons for saline administration (hypotension/cramps/access/reason not specified)	6/7/2/6	6/4/4/10	5/1/7/9	7/5/5/8
Pre-HD serum glucose (mg/dL)[b]	176.9 ± 49.1	189.7 ± 114.0	109.6 ± 17.3	112.7 ± 24.7
Pre-HD serum insulin (mU/L)[b]	45.6 ± 24.6	44.5 ± 28.4	35.4 ± 27.2	41.3 ± 31.0

[a]Data reported as mean ± SD. Data of serum glucose are reported in conventional units (mg/dL), for conversion to SI units (mmol/L) values have to be multiplied by 0.0555.
[b]Values marked were only assessed on days where blood draws where conducted (G100: 104 treatments; G200: 56 treatments). No statistically significant differences between G100 and G200 have been found.

Table 3. Diffusive and convective ($MT_{diffusive}$ and $MT_{convective}$), total mass transfer and mean serum glucose (SG_{mean}) during HD using 100 (G100) and 200 (G200) mg/dL dialyzate glucose concentrations (G100: 104 treatments; G200: 56 treatments)[a]

	Diabetic subjects				Non-diabetic subjects			
	SG_{mean} (mg/dL)	$MT_{diffusive}$ (g)	$MT_{convective}$ (g)	Total mass transfer (g)	SG_{mean} (mg/dL)	$MT_{diffusive}$ (g)	$MT_{convective}$ (g)	Total mass transfer (g)
G100	154.0 ± 27.3	−30.1 ± 14.7	−4.7 ± 1.7	−34.8 ± 16.0	106.5 ± 10.8	−5.0 ± 5.9	−2.9 ± 0.8	−7.9 ± 6.2
G200	192.8 ± 48.1	−11.6 ± 25.8	−4.9 ± 1.8	1.4 ± 27.1	127.0 ± 11.2	28.5 ± 7.0	−3.8 ± 0.8	24.8 ± 7.2
Difference G100 – G200 (95% CI)	−38.8 (−56.4 to −21.2)*	−25.2 (−32.5 to −17.9)*	1.9 (1.0 to 2.9)*	−23.2 (−31.2 to −15.2)*	−20.6 (−25.9 to −15.3)*	−33.5 (−37.6 to −28.2)*	0.8 (0.2 to 1.5)*	−32.7 (−37.2 to −28.2)*

[a]Data of serum glucose are reported in conventional units (mg/dL), for conversion to SI units (mmol/L) values have to be multiplied by 0.0555.
*$P < 0.05$.

significantly higher plasma glucose concentrations during dialyses using G200. This difference was significant throughout the whole treatment in both groups (Figure 2). SI_{mean} was significantly higher in non-diabetic subjects during G200 treatments (G100: 33.4 ± 12.6 mU/L; G200: 50.5 ± 40.3 mU/L; $P < 0.05$). Non-diabetic subjects showed significantly higher mean insulin levels at 30 min. In contrast, diabetic subjects did not show significant differences of SI_{mean} between G100 and G200, a finding which was consistent throughout the entire treatment (Figure 3).

In subjects with diabetes, hypoglycemia was observed none of the treatments with G200 and in four treatments with G100 ($P = 0.13$).

Glucose mass transfer. Diabetic subjects gained on average 1.4 ± 27.1 g of glucose during HD using G200 and lost 34.8 ± 16.0 g of glucose when using G100. In contrast, non-diabetic subjects gained 24.8 ± 7.2 g using G200 and lost 7.9 ± 6.2 g using G100 (Table 3).

Insulin mass transfer. Based on information provided by the manufacturer, the KoA of insulin was estimated to be 0.165 L/min in average, which translates into an insulin clearance between 0.103 and 0.122 L/min, depending on the individual blood and dialyzate flow rates. The estimated insulin clearances allowed us to calculate the intradialytic insulin removal in the 14 diabetic (G200: 0.9 ± 0.4 IU; G100: 0.9 ± 0.4 IU per treatment, n.s.) and 15 non-diabetic

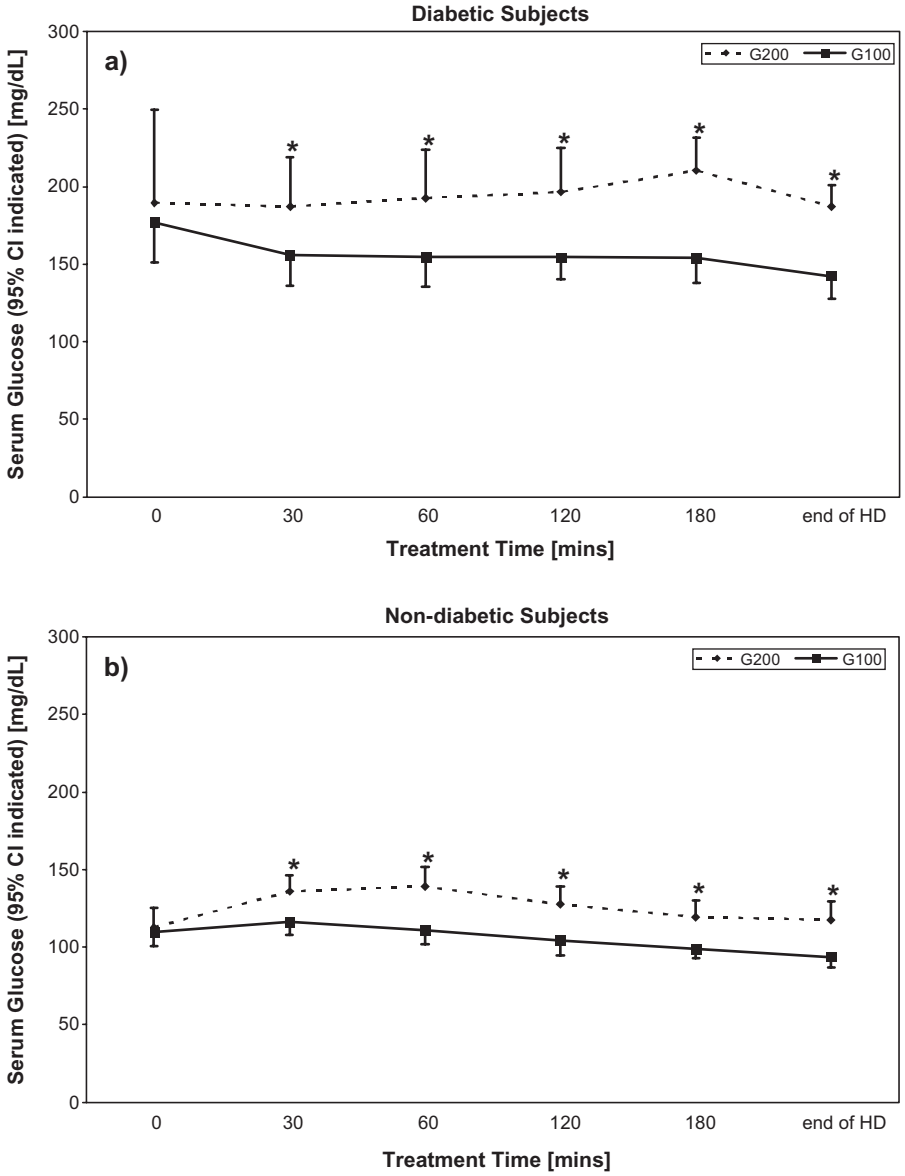

Fig. 2. Serum glucose concentrations during HD using dialyzate glucose concentrations of 100 mg/dL (G100, depicted as circles connected with a full line) and 200 mg/dL (G200, depicted as rhomboids connected with a dashed line) in (**a**) diabetic ($n = 14$, on the left) and (**b**) non-diabetic subjects ($n = 15$, on the right). Data of serum glucose are reported in conventional units (mg/dL), for conversion to SI units (mmol/L) values have to be multiplied by 0.0555. *$P < 0.05$.

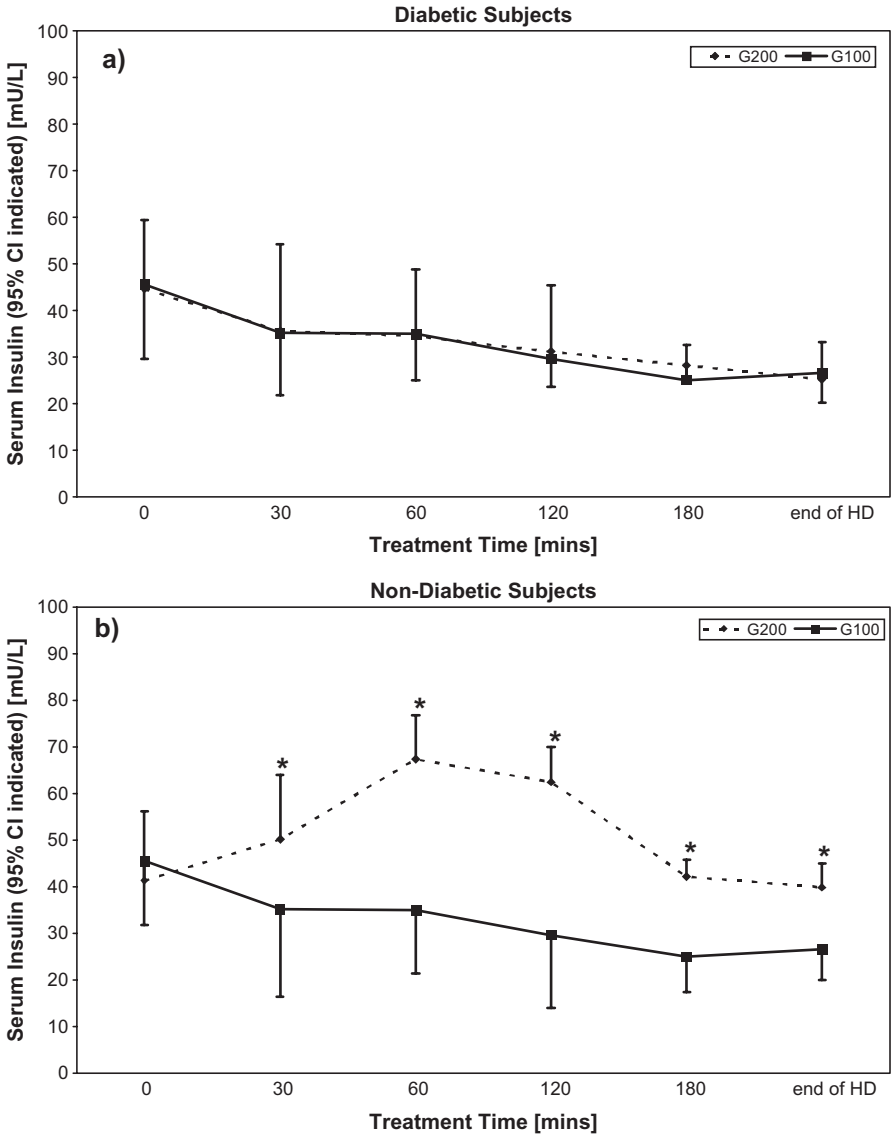

Fig. 3. Serum insulin concentrations during HD using dialyzate glucose concentrations of 100 mg/dL (G100, depicted as circles connected with a full line) and 200 mg/dL (G200, depicted as rhomboids connected with a dashed line) in (**a**) diabetic ($n = 14$, on the left) and (**b**) non-diabetic subjects ($n = 15$, on the right). *$P < 0.05$.

subjects (G200: 1.5 ± 0.9 IU; G100: 1.0 ± 0.5 IU per treatment, n.s.).

Potassium/phosphorus. Mean serum potassium levels did not show substantial differences between G100 and G200 at any time point (Table 4). In diabetic subjects, P concentration at the end of HD was slightly lower with G100 (G100: 1.9 ± 0.4 mg/dL; G200: 2.1 ± 0.3 mg/dL; $P < 0.05$) (Table 5). In non-diabetic subjects, early decline in P was more pronounced with G100.

IDWG, SBP, Holter recordings and adverse events

SBP (Figure 4; Table 6) and intradialytic adverse events did not differ significantly between G100 and G200 (Table 2). IDWG was not affected by dialyzate glucose. Cardiac arrhythmias (supraventricular and ventricular tachycardia and ventricular extrasystolic beats) did not differ between G100 and G200.

Sensitivity analysis

Exclusion of (i) patients not receiving insulin and/or antidiabetic medication ($n = 2$) and (ii) treatments where food was ingested in the very beginning of the HD treatment (G100: 23 treatments and G200: 14 treatments) did not alter the results materially (data not shown).

Discussion

To the best of our knowledge, this is the first RCT to compare the metabolic effects of G200 and G100 during dialysis. The main findings are significantly lower

Table 4. Serum potassium (K^+) concentrations in diabetic and non-diabetic patients at the beginning, after 120 min and at the end the end of HD and the temporal changes during the course of HD treatments using 100 (G100) and 200 mg/dL (G200) dialyzate glucose (G100: 104 treatments; G200: 56 treatments)[a]

	Pre-HD K^+	$K^+_{120\ min}$	$K^+_{end\ HD}$
Diabetic subjects			
G100	4.8 ± 0.4	3.6 ± 0.5	3.5 ± 0.2
G200	5.2 ± 0.9	3.7 ± 0.4	3.5 ± 0.2
Difference G100 – G200 (95% CI)	−0.4 (−1.0 to 0.2)	−0.1 (−0.3 to 0.1)	0 (−0.1 to 0.2)
Non-diabetic subjects			
G100	4.9 ± 0.5	3.5 ± 0.5	3.6 ± 0.3
G200	4.8 ± 0.4	3.5 ± 0.4	3.3 ± 0.4
Difference G100 – G200 (95% CI)	0.1 (−0.1 to 0.3)	0 (−0.2 to 0.2)	0.3 (−0.1 to 0.7)

[a]No statistically significant differences between G100 and G200 have been found.

Table 5. Serum phosphorus (P) concentrations in diabetic and non-diabetic patients at the beginning, after 120 min and at the end and the temporal changes during the course of HD treatments using 100 (G100) and 200 mg/dL (G200) dialyzate glucose concentrations (G100: 104 treatments; G200: 56 treatments)

	Pre-HD P	$P_{120\ min}$	$P_{end\ HD}$
Diabetic subjects			
G100	4.9 ± 0.9	2.3 ± 0.3	1.9 ± 0.4
G200	5.2 ± 0.8	2.4 ± 0.3	2.1 ± 0.3
Difference G100 – G200 (95% CI)	−0.3 (−0.9 to 0.3)	−0.1 (−0.3 to 0)	−0.2 (−0.3 to −0.1)*
Non-diabetic subjects			
G100	5.9 ± 0.8	2.6 ± 0.6	2.5 ± 0.4
G200	5.5 ± 1.2	2.6 ± 0.4	2.2 ± 0.4
Difference G100 – G200 (95% CI)	0.4 (0.0 to 0.7)	0 (−0.2 to 0.2)	0.4 (0.0 to 0.7)

*$P < 0.05$.

glucose shifts from the dialyzate to the subject's blood with the use of G100 and correspondingly lower SG and SI levels without effects on hemodynamic stability and without the occurrence of symptomatic hypoglycemic events.

The interpretation of the intradialytic glucose and insulin levels has to consider the insulin removal via the dialyzer [14, 15] and also a large variability of SG and SI levels between the studied subjects. It has been proposed recently that insulin removal is mainly due to adsorption and not due to dialysis [16]. If this is correct, our insulin removal estimate may be to some extent inaccurate. Notwithstanding these considerations, insulin removal by the dialyzer is likely to result in an increased insulin secretion in non-diabetic subjects. The basal insulin secretion rate ranges from 15 to 18 mU/min in healthy subjects [17], which translates to ~3.5–4.5 IU over the course of an HD treatment. Insulin secretion can be increased up to a total of 1.4 IU/12.5 g of ingested glucose in healthy subjects [17]. Insulin removal via the dialyzer in tandem with failure to adequately increase insulin secretion despite the presence of hyperglycemia may contribute to the steady intradialytic decline of insulin levels observed in diabetic subjects (Figures 2 and 3). The absence of significant differences in insulin concentrations between G100 and G200, despite significant differences in glucose concentrations, may indicate impaired insulin secretion. To what extent the uremic milieu affects insulin secretion and contributes to defective beta cell function, as suggested by several authors [18, 19], warrants future studies.

Average serum glucose levels over the course of HD were significantly higher with G200 as compared to G100 (Figure 2). This is readily explained by a larger glucose gradient between dialyzate and blood, which results in a diffusive flux of glucose into the patient (Table 3). In diabetic subjects, this resulted in a glucose mass transfer in the range of −159 g to 22 g (−636 to 88 calories) with G200 and −158 to −4 g (−632 to −16 calories) with G100. In non-diabetic subjects, glucose mass transfer ranged from 1 to 37 g (4 to 148 calories) with G200 and −14 to 10 g (−56 to 40 calories) with G100. Burmeister reported an average glucose removal of 16.7 g (66.8 calories)] per hour with G0 and 5.2 g (20.8 calories) per hour with G90 in diabetic and non-diabetic patients. Ward *et al.* reported a total intradialytic glucose gain with G200 between 18.2 and 20.6 g (72.8 to 82.4 calories) in diabetic and non-diabetic patients. In contrast, total glucose removal with G0 was between 27.7 and 29.3 g (110.8 to 117.2 calories) in diabetic and non-diabetic patients [2, 10]. These results show the importance of considering adequate dialyzate glucose concentration to avoid either glucose loading or excessive losses. In addition, it is important to note that this amount of glucose enters the circulation intravenously and may not adequately induce physiological reactions, such as insulin section stimulated by gastric and/or duodenal hormones (e.g. GLP-1), as compared to oral ingestion. As a consequence of blunted insulin secretion, glucose remains at higher concentrations for a longer time in the circulation, which may result in more pronounced adverse effects.

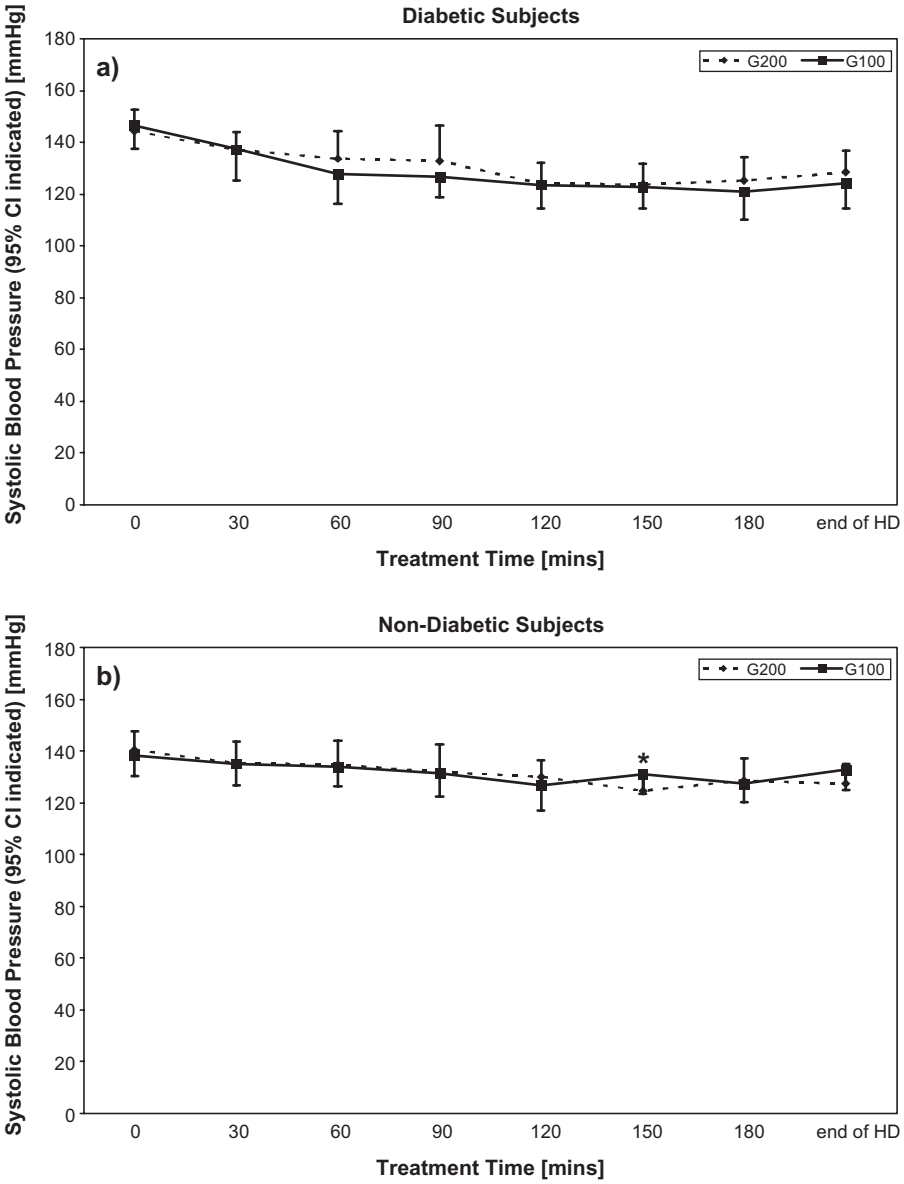

Fig. 4. SBP during HD using dialyzate glucose concentrations of 100 mg/dL (G100, depicted as rhomboids connected with a full line) and 200 mg/dL (G200, depicted as circles connected with a dashed line) in (**a**) diabetic ($n = 14$, on the left side) and (**b**) non-diabetic subjects ($n = 15$, on the right side). *$P < 0.05$.

Table 6. SBP in diabetic and non-diabetic subjects during the course of HD treatments where blood samples were obtained, using dialyzate with 100 (G100) and 200 mg/dL (G200) of glucose (G100: 104 treatments; G200: 56 treatments)[a]

	$SBP_{pre\text{-}HD}$	$SBP_{30\ min}$	$SBP_{60\ min}$	$SBP_{120\ min}$	$SBP_{180\ min}$	$SBP_{end\ HD}$
Diabetic subjects						
G100 SBP (*t*)	146 ± 17	137 ± 23	128 ± 22	124 ± 17	121 ± 19	124 ± 19
G200 SBP (*t*)	144 ± 16	137 ± 13	134 ± 20	124 ± 15	125 ± 17	128 ± 16
Difference G100 − G200 (95% CI)	2 (−6 to 10)	0 (−8 to 9)	−6 (−17 to 5)	0 (−9 to 8)	−3 (−11 to 5)	−4 (−13 to 5)
Non-diabetic subjects						
G100 SBP (*t*)	138 ± 15	135 ± 16	133 ± 15	126 ± 19	127 ± 14	132 ± 15
G200 SBP (*t*)	140 ± 14	135 ± 17	135 ± 18	130 ± 12	129 ± 15	127 ± 15
Difference G100 − G200 (95% CI)	−2 (−7 to 3)	0 (−7 to 7)	−1 (−7 to 5)	−3 (−11 to 5)	−10 (−31 to 12)	8 (−2 to 19)

[a]No statistically significant differences between G100 and G200 have been found.

Malnutrition is prevalent in a high percentage of chronic HD patients and it has been suggested that dialyzate glucose could serve as a means to improve nutritional status [20]. It is conceivable that highly malnourished patients may have potential benefit from the intradialytic glucose influx with G200. Nevertheless, given the discouraging results with hypercaloric intradialytic parenteral nutrition [21], we deem it unlikely that G200 would result in improved nutritional status and result in better outcomes.

Glucose mass transfer was estimated based on glucose KoA determined for the specific polysulfone high-flux dialyzer used in our study (Fresenius Optiflux F180NR).

For the calculation of glucose mass transfer, the glucose levels between two consecutive time points were interpolated by a linear function to calculate the mean glucose gradient in a given time interval. The glucose concentration between two measurements may not necessarily follow a linear function. For a more detailed understanding of intradialytic glucose and insulin kinetics, future studies may employ shorter sampling intervals and may also be validated by estimations by kinetic modeling by direct dialysis quantification (DDQ).

Post-dialytic potassium and phosphorus concentrations did not differ substantially between G100 and G200, irrespective of diabetes status (Table 4 and Table 5). This may be due to transient hyperinsulinism, which is known to cause shifts of potassium and phosphorus in the intracellular compartment. To refute the notion that G200 may result in reduced dialytic K and P removal future studies, adjusting concentrations and the resulting gradients for plasma void volume are needed. The intradialytic change in phosphorus levels was slightly lower in diabetic subjects with G200, a finding of potential clinical significance requiring further research and validation by DDQ.

Hypoglycemia has been a major concern with the use of G100 instead of G200. Our study showed no significantly different frequency of hypoglycemia with G100. All hypoglycemic episodes were asymptomatic.

Differences in activation of the autonomic nervous system during dialysis using G100 and G200 have been recently reported [22]. This and theoretical considerations of differences in osmolality raised concern for more intradialytic events, in particular hypotension, with the use of lower dialysate glucose concentrations. Our clinical results indicate no difference in SBP, intradialytic adverse events or saline use between G100 and G200 (Figure 4; Table 2 and Table 6). No difference in the occurrence of cardiac arrhythmias, which may have been caused by temporary shifts of K between the intra- and extracellular compartment, was found between both concentrations.

Hyperinsulinism as a result of G200 deserves consideration because it may induce pro-inflammatory cytokines and promote insulin resistance [e.g. via ras-related-associated-with-diabetes-gene (RRAD), serum/glucocorticoid-regulated kinase (SGK)]. Of note, hyperinsulinism as short as 4 h has been shown to induce these effects [23]. Other adverse effects of hyperglycemia are its associated cardiovascular risks [24–26] and pro-thrombotic [27, 28] and pro-inflammatory effects [29, 30]. It may be noted at this point that other studies have shown anti-inflammatory effects of insulin infusions in hospital settings [31, 32] and during the course of HD treatments [33]. However, this requires additional research and had not been a subject of this investigation.

Limitations are the small sample size, which is of particular importance in the analysis of the few hypoglycemic events, and the short study duration. Furthermore, the exact doses and the timing of the intake of insulin and anti-diabetic medication are unknown. However, since patients were blinded to the dialyzate glucose concentration, it is unlikely that doses of insulin and oral anti-diabetic drugs were changed systematically. In addition, sensitivity analysis showed no influence of anti-diabetic therapy on the results. It also needs to be noted that this study was not designed and not powered to test for differences in hypoglycemia between G100 and G200, and future adequately powered studies also investigating hard outcomes such as hospitalization and survival are warranted, including adjustments of anti-diabetic therapy with lower dialyzate glucose levels, both in patients with oral anti-diabetic drugs and insulin therapy. Trials studying hard end points could also help to answer the important question of the optimal dialyzate glucose concentration.

Measurement of triglycerides was not available in this study and may be considered in future projects. It may also be noted that it was not captured when the last meal prior to HD was ingested. However, with regard to subjects being blinded to the dialyzate they received, this is unlikely to be of significance when comparing both periods. Furthermore, sensitivity analysis excluding treatments where patients ingested food at the very beginning of dialysis also did not alter the results of the study. Finally, the mean age of the study population (54 $\pm$ 13 years) was substantially lower than that of the general US HD population (61.3 $\pm$ 15 years) [34]; in addition, study subjects were only recruited in two different urban dialysis clinics in New York City, all of which may potentially affect the external validity of this study. However, these limitations are in part outweighed by the randomized crossover design and the paired analysis. In particular, the paired fashioned analysis and the comparison of two consecutive mid-term study periods without intra-individual variability by virtually unchanged dialysis and medications prescriptions are major strengths of this study.

To our knowledge, this is the first study comparing the metabolic effects of G200 versus G100 in a randomized, prospective crossover trial. In this short-term study, HD with G100 reveals a more favorable metabolic profile both in patients with and without diabetes mellitus as compared to G200. Adverse events (intradialytic hypotension and hypoglycemia) did not differ between the two dialyzate glucose concentrations. Larger trials are necessary to further address the potential association of hypoglycemia and G100 and to investigate the effects on hard outcomes such as hospitalizations and survival.

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