Glucose-added dialysis fluid prevents asymptomatic hypoglycaemia in regular haemodialysis

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Abstract

**Background.** Hypoglycaemia (HG) has been demonstrated during chronic haemodialysis (HD). These events may become more frequent with the current use of glucose-free bicarbonate dialysis solution, the standard formula in most dialysis facilities in the last decade. On the other hand, HG-related symptoms are unusual among patients during or just after dialysis sessions. The aim of this study was to evaluate the occurrence of HG in diabetic (DM) and non-diabetic (NDM) end-stage renal failure patients during HD using dialytic solution without and with glucose.

**Methods.** Forty-two chronic renal failure patients—21 DM and 21 NDM—randomly selected among the 97 in our dialysis unit were submitted to an HD session with glucose-free bicarbonate solution (phase 1). Serum glucose was measured at 30, 60, 150 and 240 min. In eight patients (four DM and four NDM) glucose was also measured in fluid leaving the dialyser at 30, 60 and 150 min. After a week, all procedures were repeated in the same patients, this time with a 90 mg/dl glucose-added bicarbonate solution (phase 2). We compared the glucose levels and the number of symptomatic and asymptomatic HG events in each group in phases 1 and 2, using bivariate analysis methods with confidence limit of 0.95%.

**Results.** Data were expressed as mean ± SD. No patient presented any clinical evidence of HG. For all patients, the mean plasma glucose level (mg/dl) was significantly higher in phase 2 than in phase 1 (138.2 ± 96.3 vs 120.7 ± 75.9; \( P = 0.0392 \)). This occurred in DM (171.1 ± 104.5 vs 132.5 ± 71.0; \( P = 0.0067 \)), but not in NDM (101.3 ± 19.4 vs 95.2 ± 21.2; \( P = 0.06 \)). With glucose-free HD solution, 10 patients (five DM, five NDM) presented 18 measures of glycaemia under 70 mg/dl, and with glucose-added solution, only one (DM) presented two measures under 70 mg/dl—\( P = 0.0045 \) (number of patients); \( P = 0.0003 \) (number of HG measures). Among DM patients, values for HG measures in phase 1 (49.1 ± 16.2 mg/dl) were significantly lower than in phase 2 (65.0 ± 1.4 mg/dl)—\( P = 0.0139 \). For all patients, glucose was lost in HD fluid leaving the dialyser at lower values in phase 2 (5.2 ± 2.9 g/h) than in phase 1 (16.7 ± 10.9 g/h)—\( P < 0.0001 \).

**Conclusions.** Asymptomatic HG was frequent during HD when glucose-free dialysis solution was used. Glucose was lost in dialytic fluid leaving the dialyser in significantly lower amounts when using glucose-added solution than glucose-free solution. Glucose-added dialysis solution at 90 mg/dl significantly reduced the number and severity of HG episodes and although it caused higher mean glycaemia in DM patients during HD, its use seems advisable in all patients.

**Keywords:** chronic renal failure; diabetes mellitus; haemodialysis; hypoglycaemia

Introduction

Hypoglycaemia (HG) occurs in patients with chronic renal insufficiency [1,2]. In end-stage renal disease (ESRD), it has been reported more frequently than in the pre-dialytic period [3], especially during haemodialysis (HD) sessions [4–8], and even more frequently in diabetic (DM) subjects [5–8], but it is usually asymptomatic [4–6]. Probably for this reason, it has not been properly estimated.

The large number of DM patients on regular HD, as well as the progressive elevation of the mean age of people entering dialytic treatment, renders a greater number of patients much more susceptible to various kinds of complications. In this context, HG episodes could be an additional risk, especially if asymptomatic.

During the early days of HD, the dialysis fluid used to contain glucose, both to achieve hypertonicity and the consequent ultrafiltration and to prevent HG
episodes [9]. Currently, most HD facilities use a sodium bicarbonate solution that does not include glucose in its composition, which provides advantages such as cost reduction and less risk of contamination. However, the association of the high blood flow with the continuous flow of this non-glucose dialytic solution through the dialyser might lead to a loss of serum glucose through the dialysate that could be related to more frequent episodes of HG.

This study was conducted to evaluate the repercussions of a HD session on glycaemia at different times in two groups of patients—DM and non-diabetics (NDM)—using dialysis solutions with and without glucose. We also tried to evaluate glucose losses in the outflow dialysate and to establish a possible relationship between these losses and the occurrence of HG episodes.

Subjects and methods

Patients

Out of 97 patients on chronic dialysis treatment at the Renal Medicine Unit of ULBRA – Hospital Universitario, Porto Alegre – Brazil, 42 were chosen by random sampling, 21 of them were DM and 21 NDM. They fitted the inclusion (minimum 18 years old and on regular, stable dialytic treatment at that unit for the last 60 days at least) and exclusion criteria (patients with an ongoing systemic infection at the time of the study, patients hospitalized for decompensation of diabetes mellitus or any other comorbidity and those who were not able to understand the characteristics and implications of the study).

Ethics

All patients were asked to give their written consent after receiving all the necessary information, and they could refuse to participate without any kind of restriction or loss. The research project was approved by the Ethics in Research Committee at ULBRA – Universidade Luterana do Brasil.

Diabetes therapy

Twenty DM patients (out of the total of 21 enrolled in the study) were on insulin therapy. All of them had reasonably well-controlled glycaemias without significant fluctuations for the last several weeks. The patients’ dietary habits were not changed either before or during the period of the study. Previous individual regular doses of long-acting Neutral Protamin Hagedorn (NPH) mixed (porcine/bovine) insulin therapy before breakfast were maintained for all the 20 DM patients on its use, since they were not previously communicated of the day of the study.

Type of study and methods

The study was a single-blind randomized clinical trial and consisted of two phases. In phase 1, the patients of both groups (DM and NDM) were submitted to a regular 4-h HD procedure with a bicarbonate solution without glucose; in phase 2, the same patients were submitted to another dialysis session using a bicarbonate solution containing glucose 90 mg/dl. There was a 1-week interval between each of the phases, and the study was always performed during the midweek dialysis session. All patients used Belco Multimat® equipment with polysulphone Fresenius® F7 and F8 dialysers, reprocessed and reused up to 12 times (according to the rules of the Brazilian Ministry of Health). For phase 1, we used our regular glucose-free bicarbonate dialysis solution from Salbego-Maniformula® (Porto Alegre, Brazil). For phase 2, we used a specially prepared glucose-added solution (90 mg/dl in the final dialytic fluid) from the same manufacturer.

HG was defined as serum glucose level below 70 mg/dl with or without symptoms.

The patients were allowed to eat during the dialysis, but no one did. They were carefully observed directly by the researchers for any sign or symptom of HG throughout the period of the sessions. If there was any suspicion of such a situation, they were submitted to capillary glycaemia evaluation using a glucometer. If capillary glycaemia below 70 mg/dl was found, the patient was medicated appropriately.

Blood and dialysate sample collections

The blood glucose level of each patient was measured four times during the HD session—at 30, 60, 150 and 240 min (end of the session). For this purpose, blood samples were collected from the arterial line of the dialysis system, e.g. coming from the patient immediately before entering the dialysis circuit.

The glucose level in the effluent fluid of the dialyser was measured during both phases of the study in eight randomly chosen patients, four DM and four NDM. Fluid was collected directly at the point of exit from the dialysate during the same dialysis sessions in which the glycaemias were collected—at 30, 60 and 150 min.

Laboratory tests

Plasma and dialytic fluid glucose level were measured by an enzymatic method in a spectrophotometer. In phase 2, we took as outflow glucose level the total glucose value measured minus the basal (background) content of the dialytic fluid.

Statistical analysis

Bivariate analysis was performed using SPSS software. Data are expressed as mean ± SD. The Fisher’s exact test was used for comparison of categorical variables. Student’s t-test was used to compare continuous variables. Statistical significance was set at \( P < 0.05 \).

Results

Study population

No significant differences were observed among the patients in the DM and NDM groups with respect to
gender, age, body mass index (BMI), serum albumin, total cholesterol and pre-dialysis urea (Table 1).

**Hypoglycaemia analysis**

No patient presented any clinical manifestation that could be related to HG at any time during the two phases of the trial.

In phase 1, HG occurred at all times when blood glucose was measured, e.g. at 30, 60, 150 and 240 min (Table 2). The number of patients who presented HG episodes during phase 1 (10 patients) was higher than in phase 2 (one patient) \((P=0.0045)\), as was the number of HG (18 \(v.s\) 2, respectively) \((P=0.0003)\) (Table 2).

The mean blood glucose level for the HG measures was lower in phase 1 than in phase 2, both among all patients \((P=0.0074)\) and specifically among the DM group \((P=0.0139)\), since no NDM had any HG measure in phase 2. For all patients, the mean (all measures) blood glucose level was higher in phase 2 than in phase 1 \((P=0.0392)\). This was observed specifically in the DM \((P=0.0067)\), but not in the NDM \((P=0.06)\) (Figure 1). The lowest blood glucose levels in phase 1 were 21 and 60 mg/dl (among the DM and NDM, respectively); in phase 2, the lowest value was 64 mg/dl (DM).

**Loss of glucose in dialysate**

For all patients, the loss of glucose (g/h) in the effluent fluid from the dialyser was higher in phase 1 \((16.7 \pm 10.9)\) than in phase 2 \((5.2 \pm 2.9)\) \((P<0.0001)\), once the glucose contained in the dialysate itself (in phase 2) had been deducted. This was observed both among the DM \((18.5 \pm 10.6 \ v.s\ 8.5 \pm 4.9; \ P=0.0003)\) and the NDM patients \((15.4 \pm 12.0 \ v.s\ 2.2 \pm 0.3; \ P<0.0001)\) (Figure 2).

No significant relationship was found between the timed loss of glucose in the dialysate and the moment of the HG measures, or even the plasma glycaemic levels.

**Discussion**

The lowest normal value for fasting blood glucose in our laboratory is 65 mg/dl, but we established HG as under 70 mg/dl according to studies that showed this to be the level at which the first changes occur as a result, such as deterioration of the auditory evoked potential [10], or initial physiological changes of the \(\alpha\) and \(\beta\)-cells of the pancreas [11].

When we used a glucose-free dialytic solution, 10 patients (five DM and five NDM)—23.8% of all 42—presented at least one measure of glycaemia below 70 mg/dl. Jackson et al. [4] found glycaemia measures below 72 mg/dl in nine patients (42.8%) of 21 NDM and in seven (33.3%) among 21 DM [5] during a single dialysis session with glucose-free solution. They observed that an NDM patient presented the lowest value \((38 \ v.s\ 50 \ mg/dl \ for \ a \ DM)\), while in our patients it was 21 mg/dl for a DM and 60 mg/dl for an NDM patient. Our data indicate a possible higher risk of DM patients developing more intense HG (Table 2), what

### Table 1. Characteristics of the patients (DM and NDM) and laboratory parameters (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>NDM</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F; n)</td>
<td>13/8</td>
<td>15/6</td>
<td>0.734**</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.5 ± 15.5</td>
<td>58.0 ± 17.0</td>
<td>0.6212**</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 ± 5.8</td>
<td>24.4 ± 4.0</td>
<td>0.3043**</td>
</tr>
<tr>
<td>Months in dialysis</td>
<td>30.4 (17)</td>
<td>51.1 (39)</td>
<td>0.6304**</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>3.73 ± 0.51</td>
<td>3.85 ± 0.50</td>
<td>0.4459**</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>173.0 ± 56.5</td>
<td>161.1 ± 44.2</td>
<td>0.4554**</td>
</tr>
<tr>
<td>Pre-dialysis urea (mg/dl)</td>
<td>113.4 ± 38.3</td>
<td>117.7 ± 36.3</td>
<td>0.8518**</td>
</tr>
</tbody>
</table>

*Fisher’s test; **t-test.

### Table 2. Number of HG measurements (and mean ± SD; mg/dl) in each moment of the dialysis, number of patients (pts) with HG and total number of blood glucose measurements (total BG) in DM and NDM patients in each phase \(n\) = number of patients in each group and phase

<table>
<thead>
<tr>
<th>HG measurements(min)</th>
<th>DM</th>
<th>NDM</th>
<th>All</th>
<th>No. of Pts.</th>
<th>Total BG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>60</td>
<td>150</td>
<td>240</td>
<td>All</td>
</tr>
<tr>
<td>Phase 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>((n=21))</td>
<td>(42.7 ± 23.1)</td>
<td>(36.5 ± 4.9)</td>
<td>(57.5 ± 12.0)</td>
<td>(60.0)</td>
<td>(49.1 ± 16.2)****</td>
</tr>
<tr>
<td>((n=21))</td>
<td>(68.0)</td>
<td>(66.3 ± 4.6)</td>
<td>(62.0 ± 1.7)</td>
<td>(60.0)</td>
<td>(64.8 ± 3.7) 18*</td>
</tr>
<tr>
<td>All ((n=42))</td>
<td>(49.0 ± 22.7)</td>
<td>(54.4 ± 16.8)</td>
<td>(59.4 ± 8.9)</td>
<td>(60.0)</td>
<td>(54.3 ± 15.2)****</td>
</tr>
<tr>
<td>Phase 2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>((n=20))</td>
<td>(64.0)</td>
<td>(66.0)</td>
<td>(65.0 ± 1.4)****</td>
<td>(65.0 ± 1.4)****</td>
<td></td>
</tr>
<tr>
<td>((n=20))</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All ((n=40))</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

\(*P=0.0003; \ **P=0.0045 \ (Fisher’s \ test); \ ***P=0.0139; \ ****P=0.0074 \ (t-test).\)
seems coherent, as this group is probably more susceptible due to their metabolic, hormonal, nutritional and therapeutic characteristics.

When we used a glucose-added dialysis solution, the number of HG episodes was significantly reduced, and occurred only in a single DM patient. Moreover, the lowest value observed was 64 mg/dl, much less impressive than those recorded when using glucose-free dialytic solution. In the two observations by Jackson et al. [4,5], when only the patients who had presented HG

Fig. 1. Mean blood glucose under 70mg/dl and mean all blood glucose measurements in Phase 1 and in Phase 2 in DM, NDM, and in all patients. Data expressed as mean ± SD (t-test).

Fig. 2. Glucose losses (g/hour) in the effluent fluid from the dialyzer for DM, NDM, and all patients in each phase. Data expressed as mean ± SD (t-test)
were redialysed with a glucose-containing solution, no HG episode was observed during the first 60 min of the sessions. Simic-Ogrizovic et al. [7], in a prospective cross-over study with DM on HD, found that, even using a dialytic fluid with glucose at 100 mg/dl, episodes of HG occurred and were more frequent than when using another fluid with glucose at 200 mg/dl. Surprisingly, though, this result reinforces the likely importance of the use of glucose in the dialytic solution, especially with DM.

Our findings showed a tendency to the occurrence of HG throughout the period of the HD session. Jackson et al. [4,5] studied only the first hour of dialysis because they considered that the main biochemical changes would occur during this period. We observed that 50% of all HG measures occurred in the initial 60 min of dialysis, but other episodes were found in every moment when we measured the blood glucose levels (Table 2).

Our results are in agreement with previous reports, where asymptomatic HG has been described as common in patients under regular HD [3–8,12]. These HG episodes are more meaningful if we take into account that no patient presented remarkable clinical manifestations, a finding already reported by Jackson et al. [4,5]. The frequent repetition of HG in DM has already been identified as a cause for the diminished clinical manifestations and neurohumoral response of patients to low blood glucose levels [13], and HG without related symptoms was demonstrated to be more frequent in normal individuals when these hypoglycaemic episodes were repeated [11]. In animals, the maintenance of low glycaemia levels for long periods increases the brain cell capacity to take up glucose, a possible explanation for this asymptomatic condition [12]. These two characteristics—a frequent repetition of the HG episodes and the lack of clinical manifestations—expose these patients, especially the DM, to the risk of a progressively compromised cognitive function [7,10,13–16].

In our patients, HD with glucose-free solution was related to significant loss of glucose in dialytic effluent fluid, and was higher in the DM (18.5 g/h) than in the NDM (15.4 g/h) (Figure 2). Jackson et al. [4,5] also observed a higher loss in DM (9.2 g/h) than in NDM patients (6.0 g/h) studying only the first 60 min of the session, and did not find a direct relationship between the amount of glucose lost and HG measures, but associated the glucose loss rates to the mean glycaemia of each patient.

There may be many other causes for these frequent HG episodes. Foss et al. [17] demonstrated that insulin resistance characteristic of chronic uraemia is accompanied by impaired muscle glucose uptake and non-oxidative glucose metabolism, which are significantly improved by HD. Takahashi et al. [8] described an excessive consumption of glucose as being the result of an accelerated anaerobic metabolism in these patients which, added to the loss of glucose itself through the effluent fluid from the dialyser, would increase the likelihood of HG—symptomatic or not. Thus, these authors proposed the use of dialysate with glucose in order to reduce the anaerobic metabolism and interrupt a vicious circle that culminates in short-term HG and long-term neurological deficits [7,8,10,14,16].

**Conclusion**

In spite of the limitations of our trial (small number of patients, different number of times each dialyser was reused before the study, limited number of blood glucose levels measurements, different schedule of dialysis—morning, afternoon and night—in relation to the time of insulin administration) and whichever the mechanism of these asymptomatic HG episodes, it is our opinion that the use of a dialytic solution with 90 mg/dl glucose appears to offer more advantages than disadvantages. Although it causes increased glycaemia in DM during dialysis, it significantly reduces the incidence of HG (which is usually asymptomatic) both in these patients and in NDM. Deleterious metabolic effects resulting from the presence of glucose in the dialytic solution were not found in short-term observations [7], but longer prospective studies would be necessary to evaluate this possibility.

**Conflict of interest statement.** The authors declare, that the results presented in this article have not been published previously in whole or part, except in abstract format at the ERA–EDTA Congress (Istanbul, 2005).

**References**


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