THE ASSOCIATION BETWEEN GLUCOSE EXPOSURE AND THE RISK OF PERITONITIS IN PERITONEAL DIALYSIS PATIENTS

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◆ **Background and objective:** Little or no clinical evidence is available on the association between glucose exposure and peritoneal host defense in peritoneal dialysis (PD) patients. The objective of the present study was to quantify the exposure to glucose during the first year on PD and investigate the association with subsequent peritonitis.

◆ **Methods:** We analyzed prospectively collected demographic and peritonitis data from incident adult PD patients between 1990 and 2010. For the present study, we conducted a review of both in- and outpatient medical records of all patients to obtain their day-to-day dialysis schemes during the first year on PD. From these data, the average exposure to glucose was quantified. The exposure was stratified into low- and high-glucose groups based on the median, analyzed per standard deviation and in quartiles. Cox proportional hazard models were used to calculate crude and adjusted hazard ratios (HRs) and 95% confidence intervals for the association between glucose exposure and peritonitis. Adjustments were made for age, sex, primary kidney disease, diabetes mellitus, Davies comorbidity score and the treatment period.

◆ **Results:** In total, 230 patients were included in the study of whom 151 (66%) experienced a first peritonitis episode. The median follow-up time was 2.6 years (interquartile range [IQR]: 1.9 – 3.8) in the low-glucose group and 3.1 (IQR: 2.1 – 4.2) in the high-glucose group. After adjustment for confounding factors, no association between high glucose exposure and the risk of peritonitis was found (HR: 0.81; 0.55 – 1.17). No association was present when glucose exposure was analyzed per standard deviation (SD) (HR: 0.98; 0.79 – 1.21) or patient quartiles were applied. No association was identified between glucose exposure and severe peritonitis, *Staphylococcus aureus* peritonitis, or a peritonitis episode that lasted more than 14 days.

◆ **Conclusions:** Exposure to glucose is not associated with an increased risk of peritonitis. The equilibrium between glycemic harm to peritoneal host defense and detrimental effects of glucose on invading microorganisms may determine the susceptibility to peritoneal infection.

KEY WORDS: Peritoneal dialysis; glucose exposure; peritonitis; host defense.

Long-term exposure to dialysis solutions causes structural changes to the peritoneum in peritoneal dialysis (PD) patients (1). The unphysiological composition of the dialysate has been hypothesized to compromise peritoneal host defense. Many *in vitro*, *ex vivo* and animal studies have been performed to investigate this hypothesis (2–5). These studies point to the detrimental effects of acidic pH, glucose, hyperosmolality, lactate buffer, and glucose degradation products (GDPs) on monocytes, peritoneal macrophages, neutrophils, and mesothelial cells. However, the majority of these studies cannot be translated to the clinical situation due to a lack of follow-up, non-realistic exposure levels, or the absence of renal failure. Over the last decade, multiple randomized controlled trials (RCTs) have been performed to compare the incidence of peritonitis between patients randomized to a high- or low-GDP regimen (6–15) and, when meta-analyzed, found no difference (16). Bicarbonate buffering reduced the length of time to peritonitis in a RCT (17), but these results still need to be confirmed in other populations. Indirectly, RCTs that compared icodextrin with glucose for the long dwell investigated a glucose-sparing vs a non-glucose-sparing regimen and reported no difference in peritonitis episodes between the 2 arms (18–21). Therefore, the composition of the dialysate appears to be harmful in non-clinical experiments, but clinical studies demonstrate otherwise.

None of the clinical studies that investigated glucose exposure and the incidence of peritonitis quantified the exposure to glucose and assessed a dose-response relationship. Furthermore, the literature concerning quantification of glucose exposure used calculations that can only be applied to continuous ambulatory PD (CAPD) patients and provide very rough estimates of the actual glucose exposure (22,23). Therefore, it is unknown whether the estimated glucose exposure is associated with an increased susceptibility to peritonitis in patients. The objective of the present study was to quantify the exposure to glucose during the first year on PD and to investigate the association with subsequent peritonitis. Our hypothesis was that exposure to higher concentrations of glucose is associated with an

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increased risk of peritonitis and a shorter time to the first peritonitis episode.

MATERIALS AND METHODS

STUDY DESIGN

The present study was conducted in a large prospective database of incident PD patients, aged >18 years, receiving dialysis in a Dutch tertiary-care university hospital between January 1990 and July 2010. All patients were treated with solutions obtained from Baxter Healthcare S.A. (Castlebar, Ireland). Data on baseline demographics and peritonitis episodes were collected prospectively in the database as part of routine clinical care. For the present study, we conducted a review of both in- and outpatient medical records of all patients to obtain their prescribed day-to-day dialysis schemes during the first year on dialysis. Patients who remained less than 1 year on PD were excluded, because we could not obtain complete information about glucose exposure during their first year on PD. Patients with peritonitis during the first year on PD were excluded to avoid an effect of peritonitis on exposure. Time of follow-up was defined as the number of days between the first 365 days on PD and the date of censoring.

DEMOGRAPHIC DATA COLLECTION

Routinely collected demographic data at the start of PD included dialysis modality (CAPD/automated PD [APD]), age, sex, and primary kidney disease. Additional data collected during the review of medical records included diabetes mellitus, Davies comorbidity score (24), the use of an angiotensin-converting enzyme inhibitor (ACE), and the use of an angiotensin II receptor blocker (ARB). Because no data on 24-hour urine urea and creatinine were available, we used serum beta-2-microglobulin to estimate residual renal function. It is known from the literature that this parameter can be used to estimate residual glomerular filtration rate (25).

GLUCOSE EXPOSURE

Day-to-day dialysis schemes were retrospectively collected in a large database. Those between 0 and 180 days on PD were neglected because this is a period in which the PD scheme is often not stable, due to adjustments required by the patients' transport status and hydration state. On a day without information on the dialysis scheme, it was assumed that the scheme of the previous day was followed. Data collected about the dialysis schemes of CAPD patients included the number of dwells per day, dwell volume, glucose concentration, the dwell time, and the type of dialysis solution. Data collected for APD patients included the total treatment volume, total treatment time, number of cycles, tidal percentage, dwell volume and glucose concentration per cycle, and dwell volume and glucose concentration of the last bag. From these data, the average exposure to glucose during 24 hours between 180 and 365 days

can be quantified. Three assumptions were made for the quantification of the glucose exposure: 1) Glucose absorption from the peritoneal cavity averages 60% after 4 hours (26); 2) glucose absorption follows first order kinetics, which means that it becomes linear after logarithmic transformation; 3) the geometric mean of glucose exposure in the middle of the dwell is the closest approximation of the average glucose exposure during the total dwell. The following calculation can be made for the geometric mean glucose concentration of a 4-h dwell: $\ln G_m = \ln(G_i) + (\ln(0.4G_i) - \ln(G_i))/2$. In this equation $\ln G_m$ is the natural logarithm of the geometric mean glucose concentration, G_i is the initial dialysate glucose concentration and 0.4 indicates that after 4 hours only 40% of the initial glucose concentration is present. The initial glucose concentration for 1.36% glucose is 70 mmol/L, for 2.27% glucose is 118 mmol/L and for 3.86% glucose is 198 mmol/L. Calculation of G_m for any dwell time can be done using $e^{\ln G_m}$. The average glucose exposure during 24 hours is the sum of all G_m values of each dwell multiplied by the fractional duration of the dwell per 24 hours. Examples are given in Supplemental Appendix 1.

STATISTICAL ANALYSES

Baseline characteristics were stratified according to the median of the glucose exposure. Continuous data are expressed as mean values and standard deviations (SD) or median and interquartile ranges (IQR) as appropriate and categorical variables in proportions. Differences between baseline characteristics were tested with an unpaired Student's *t*-test, Mann-Whitney (continuous data), or chi-square test (categorical data). Unadjusted cumulative survival curves over a period of 5 years according to high and low glucose were calculated, with the first peritonitis episodes, death, switch to hemodialysis (HD), and transplantations as the events.

Cox proportional hazard models were used to calculate crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the association between glucose exposure and peritonitis. For these analyses, glucose exposure was stratified into high or low exposure based on the median, assessed per SD and in quartiles. Violation of the proportionality assumption in the Cox models was checked by making log-minus-log plots. No violations were observed. Adjustments were made for age, sex, primary kidney disease, diabetes mellitus, Davies comorbidity score, and the treatment period (1990–1996 (Dianeal; Baxter Healthcare SA, Castlebar, Ireland, only), 1997–2004 (transition period and introduction of icodextrin), 2005–2010 (Physioneal; Baxter Healthcare SA, Castlebar, Ireland only)). Additional Cox proportional hazard models were used to calculate crude and adjusted HRs and 95% CIs for the association between glucose exposure and severe *Staphylococcus aureus* or long-lasting peritonitis. For these analyses, glucose exposure was stratified into high or low exposure. Severe peritonitis was defined as a leukocyte count > 1,090 cells/mm³ on day 3 or > 100 cells/mm³ on day 5 of the peritonitis episode (27) and compared with patients without severe peritonitis. Causative microorganisms were dichotomized in

Staphylococcus aureus and compared with patients who did not suffer from *Staphylococcus aureus* peritonitis. The duration of the peritonitis episode was calculated and dichotomized in long duration (> 14 days) and compared with patients who did not experience a first peritonitis episode that lasted longer than 14 days. All data analyses were performed using SPSS 20.0 (SPSS, Chicago, IL, USA) and STATA 12.1 (StataCorp LP, College Station, TX, USA).

SENSITIVITY ANALYSES

Sensitivity analyses with less strict inclusion criteria were performed to demonstrate whether the results could change when: 1) dialysis schemes were included from day 1 on PD; 2) a study baseline of 3 months or 6 months was used and consequently; 3) the majority of the first peritonitis episodes during the first year on PD could be included in the analysis. The influence of CAPD/APD on peritonitis risk is uncertain and therefore is a confounder (28,29). A sensitivity analysis was performed, in which modality (CAPD/APD) at the start of dialysis was added to the fully adjusted model to explore its influence on the association. Residual renal function at the start of dialysis might be a confounder of the association. However, this information was available in a limited number of patients ($n=99$). Therefore, residual renal function according

to serum beta-2-microglobulin was added to the model in a sensitivity analysis to examine its impact on the association.

RESULTS

POPULATION CHARACTERISTICS

Medical records of 479 incident patients starting PD treatment between January 1990 and July 2010 in our center were reviewed. After excluding patients with incomplete or lost files ($n=39$) or less than 1 year until peritonitis or censoring ($n=210$) a total of 230 patients could be included. The baseline characteristics of the study population are summarized in Table 1. The median and mean of the glucose exposure between 6 and 12 months was 44 mmol/L during 24 hours with a SD of 18. Patients with a higher glucose exposure were more often treated with CAPD and had lower residual renal function. The median follow-up time was 2.6 years (IQR: 1.9 – 3.8) in the low-glucose group and 3.1 (IQR: 2.1 – 4.2) in the high-glucose group. Of all patients, 147 (64%) experienced a first peritonitis episode, of which 77 were treated with low glucose exposure and 70 with high glucose exposure. The main reasons for censoring in patients without peritonitis were death (low glucose: 14%; high glucose: 16%) and transplantation (low glucose: 13%; high glucose: 11%) (Figure 1).

TABLE 1
Baseline Demographic Characteristics

Characteristic	'Low exposure' Glucose exposure <44 mmol/L/24 h	'High exposure' Glucose exposure ≥ 44 mmol/L/24 h	P value
No of patients (%)	115	115	
Age (median (IQR))	54 (42–67)	57 (44–66)	0.93
Sex (% male)	64	58	0.42
Diabetes (%)	29	33	0.48
Primary kidney disease (%)			0.14
Diabetic nephropathy	24	29	
Glomerulonephritis	18	24	
Renal vascular disease	20	17	
Other	37	30	
Davies comorbidity score (% severe)	9	8	0.85
Dialysis modality (%)			0.002
CAPD only	41	72	
APD only		23	7
CAPD switched to APD	33	17	
APD switched to CAPD	4	4	
ACE/ARB usage (%)			0.17
ARB only	4	4	
ACE only	46	44	
ACE + ARB	12	5	
Serum β -2 microglobulin (mg/L)*	19.9±7.0	23.4±8.8	0.03
Glucose exposure (mmol/L/24 h; median (IQR))	27 (21–33)	51 (46–61)	<0.001
Time on PD (years; median (IQR))	2.6 (1.9–3.8)	3.1 (2.1–4.2)	0.11

IQR = interquartile range; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; ACE = angiotensin I converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

* At baseline and available in a limited number of patients ($n=99$).

Time after start PD (d)	365	730	1095	1460	1825	365	730	1095	1460	1825
N at risk	115	79	38	20	0	115	84	51	25	3

Figure 1 — Unadjusted cumulative incidence survival curves for peritonitis-free survival, peritonitis, switch to HD, transplantation, and death on PD for patients exposed to low and high glucose exposure. HD = hemodialysis; PD = peritoneal dialysis; d = days.

GLUCOSE EXPOSURE AND PERITONITIS

Figure 1 shows the unadjusted cumulative incidence survival curves. No difference in the crude peritonitis-free survival was observed between the patients exposed to high and low glucose. Table 2 shows crude and adjusted HRs and 95% CIs for high vs low glucose exposure, per glucose SD and in patient quartiles. The unadjusted HRs demonstrated a consistent trend that is suggestive of a protective association between higher glucose exposure and peritonitis. However, when adjustments for confounding factors were made, the trend toward an association lost statistical significance. High glucose exposure remained associated with a 19% lower risk of peritonitis compared with low glucose exposure, but the CI was fairly wide and could indicate both a 45% decreased risk and a 17% increased risk of peritonitis in the high exposure group. Also, no association was present when glucose exposure was evaluated per SD or when patient quartiles were applied.

SEVERITY, CAUSATIVE MICROORGANISM, AND DURATION OF THE PERITONITIS EPISODE

Of all first peritonitis episodes, 74 lasted longer than 14 days, 26 could be qualified as a severe peritonitis episode, and in 25 of the cases, *Staphylococcus aureus* was the causative microorganism. Supplemental Appendix 2 shows the distribution of the causative microorganisms in the low and high glucose exposure groups. Unadjusted HRs were non-significant with a large confidence interval for severe peritonitis (HR: 0.71; 95% CI: 0.46 – 1.10), *Staphylococcus aureus* peritonitis (0.83; 0.40 – 1.72), or a peritonitis episode that lasts more than 14 days (0.71; 0.55 – 0.91). The low event rate of severe and *Staphylococcus aureus* peritonitis made further adjustments impossible. However, when adjustments were made, high glucose exposure might lead to a 14% decreased risk of a peritonitis episode that lasted more than 14 days, but the CI was fairly wide and remained non-significant (0.86; 0.63 – 1.17).

SENSITIVITY ANALYSES

When less strict inclusion criteria were used, the results did not change when dialysis schemes were included from day 1 on PD and the study baseline was set at 3 months (adjusted HR high vs low glucose exposure: 0.87; 95% CI: 0.65 – 1.17; adjusted HR per SD: 1.04; 95% CI: 0.89 – 1.21), 6 months (adjusted HR high vs low glucose exposure: 0.73; 95% CI: 0.51 – 1.06; adjusted HR per SD: 1.09; 95% CI: 0.86 – 1.38) or 1 year (adjusted HR high vs low glucose exposure: 0.76; 95% CI: 0.47 – 1.22; adjusted HR per SD: 1.07; 95% CI: 0.84 – 1.36). When dialysis modality (CAPD/APD) at the start of dialysis was added to the model, the HRs changed slightly, but were not significant with reasonably large CIs (high vs low HR: 0.84; 0.57 – 1.23; per SD HR: 1.01; 0.81 – 1.25). When residual renal function was added to the model, the HRs did not change.

DISCUSSION

We demonstrated a novel method for the quantification of glucose exposure that can be used in both CAPD and APD patients. The results of the present study show that glucose exposure during the first year on PD is not associated with the time to subsequent peritonitis. In addition, no association between the amount of glucose exposure and severe peritonitis, *Staphylococcus aureus* peritonitis, or a peritonitis episode that lasts more than 14 days was identified.

Our results are in line with the results from previous RCTs that compared peritonitis risk in patients treated with a glucose sparing with a non-glucose sparing regimen (18–21). They are, however, in contrast to a large body of evidence from *in vitro*, *ex vivo*, and *in vivo* studies (2–5). Two possible explanations for this phenomenon are presented. First, it might be that the experiments were unable to mimic the situation in PD patients. Experimental models often suffered from lack of follow-up, non-realistic exposure levels, or the absence of renal failure, which makes translation to clinical practice impossible. A

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TABLE 2
Crude and Adjusted HRs (95% CI) Associated with Glucose Exposure During 6–12 Months on Peritoneal Dialysis

	HR (95% CI) glucose high vs glucose low	HR (95% CI) per SD glucose	Qrt1: 0–27.0 mmol/L during 24h	Qrt2: 27.1–41.0 mmol/L during 24h	Qrt3: 41.1–51.4 mmol/L during 24h	Qrt4: 51.5–86.5 mmol/L during 24h
Crude	0.71 (0.51–0.99)	0.88 (0.74–1.05)	1.00	0.80 (0.50–1.28)	0.74 (0.46–1.18)	0.79 (0.50–1.26)
Adjusted model 1	0.72 (0.51–1.01)	0.90 (0.75–1.07)	1.00	0.77 (0.48–1.24)	0.76 (0.47–1.21)	0.82 (0.51–1.32)
Adjusted model 2	0.74 (0.53–1.03)	0.90 (0.76–1.07)	1.00	0.74 (0.46–1.19)	0.77 (0.48–1.24)	0.77 (0.48–1.24)
Adjusted model 3	0.81 (0.55–1.17)	0.98 (0.79–1.21)	1.00	0.88 (0.52–1.50)	0.97 (0.55–1.72)	0.97 (0.53–1.77)

HR = hazard ratio; SD = standard deviation; qrt = quartile; adjusted model 1 = age, sex, primary kidney disease; adjusted model 2 = + DM and Davies score; adjusted model 3 = + period effect.

second explanation might be that glucose does not only exert detrimental effects on the peritoneal host defense but also on the invading microorganisms. It could well be that the risk of peritonitis is determined by the balance between harm to the peritoneal host defense on one hand and bactericidal effects on the other.

Little is known about the glucose concentrations that are necessary to facilitate bactericidal activity in humans. *In vitro* studies investigated different honeys and honey-equivalent sugar solutions (30–35). Among other components, the high sugar concentration and its osmolality and methylglyoxal (MGO) were identified as being responsible for the bactericidal properties of these honey substances. When we compare the sugar concentrations that were found to facilitate bacterial killing in these *in vitro* experiments to the glucose concentration in a PD solution, the bactericidal sugar concentrations were much higher than the maximum glucose concentrations in dialysis solutions: about 20% vs 3.86%/4.25%. Furthermore, the osmolality that was bactericidal *in vitro* was approximately twice as high as the osmolality of a 3.86% dialysis solution: $\pm 1,000$ mOsmol/L vs 483 mOsmol/L. However, the *in vitro* bactericidal concentration and osmolality might not be comparable to the exposure necessary to cause intraperitoneal bactericidal or bacteriostatic effects. In patients, RCTs assessed the effect of topical application of honey for prevention of infections and improved wound healing (36–39). It is, however, impossible to extract an effective dosage from these studies and make a comparison to glucose in the dialysis solutions.

The antibacterial properties of MGO were discovered due to its high concentrations in Manuka honey (38–42). More interestingly, MGO is one of the glucose degradation products in Dianeal, Physioneal, and icodextrin as well as in other commercially available dialysis solutions. The concentrations of MGO are 0.5–1 $\mu\text{mol/L}$ in Physioneal, 4–7 $\mu\text{mol/L}$ in Dianeal and 2 $\mu\text{mol/L}$ in icodextrin (43), suggesting that Dianeal has the highest bacteriostatic capacity. This hypothesis is supported by a previous report by Verbrugh *et al.* (44) which showed that Dianeal, amongst other commercially available

solutions, did not support survival of *Staphylococcus aureus* and *Staphylococcus epidermidis in vitro*. In our dialysis unit, patients were treated with Dianeal between 1990 and 1997, with Dianeal or Physioneal between 1998 and 2004, and with Physioneal between 2005 and 2010. The use of icodextrin started in 1997. In our study, patients with higher glucose concentrations were more often treated with Dianeal, whereas patients with lower glucose exposure were more often treated with Physioneal and icodextrin. Therefore, our results might be influenced by a correlation between higher glucose exposure and higher MGO concentrations in our patients. This could explain the tendency of the estimates toward a protective effect of glucose exposure with respect to peritonitis risk. On the other hand, the MGO concentration differences are small and studies that compared conventional and biocompatible solutions found no difference in peritonitis risk in a meta-analysis (45).

To the best of our knowledge, we are the first to study the association between glucose exposure and severe peritonitis, *Staphylococcus aureus* peritonitis and peritonitis that lasted more than 14 days. The low event rate of severe and *Staphylococcus aureus* peritonitis limited our analyses and, although the estimates tended toward a protective effect of glucose, no association could be attributed. Higher glucose concentrations appeared to decrease the risk of a peritonitis episode that lasted longer than 14 days, but this was not statistically significant.

The present study has several strengths and weaknesses. Although demographic and clinical data and information about peritonitis episodes were collected prospectively, we retrospectively collected day-to-day dialysis schemes during the first year on PD. We are confident that a thorough review of complete original medical records was performed. However, prospective data collection would be preferred to accurately capture day-to-day glucose exposure until censoring in all patients. Because data collection was limited to the first year on PD, we are unable to draw conclusions about the influence of glucose exposure beyond the first year on PD. Although extensive adjustments were made, residual confounding

cannot be excluded due to the observational design of the study. After the year 1990, 2 changes were introduced to the treatment regimen: the application of daily mupirocin at the exit site since 2001 and the use of only biocompatible fluids since 2004. However, a previous study has shown that these changes in clinical care did not significantly influence the background peritonitis rate (46). The use of strict inclusion criteria could be seen as both a limitation and a strength of the study design.

A major strength of our study is the inclusion of incident PD patients with a long-term follow-up. In addition, a novel method was used to quantify the exposure to glucose. The major advantage of this method is that it can be used for both CAPD and APD patients. Three underlying assumptions supported the calculations. First, Krediet *et al.* (26) found that glucose absorption was approximately 60% after a 4-hour dwell. In addition, Smit *et al.* (47) showed that this was not different when dialysis solutions with different glucose concentrations were used or when patients suffered from diabetes (48). Although the calculation of glucose exposure could be improved by the substitution for 60% in the equation of the individual measured glucose exposure, the use of 60% is easy and fairly accurate (47). Second, the assumption that glucose absorption during a PD dwell follows first order kinetics has previously been established (49,50). Consequently, we assumed that the geometric mean of glucose exposure in the middle of the dwell is the closest approximation of the average glucose exposure during the total dwell.

In conclusion, our study demonstrated no association between glucose exposure during the first year on PD and the subsequent time to peritonitis. This is in line with previous studies in patients. However, an overall tendency towards a protective effect of higher glucose concentrations was observed, although this was not significant in the majority of the analyses. It could well be that the risk of peritonitis is determined by the balance between the harm of dialysis solutions to peritoneal host defense on one hand and their bactericidal effects on the other. Future studies should determine whether bactericidal properties of PD solutions might have a clinically relevant function in the prevention of peritonitis.

DISCLOSURES

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