A Model To Estimate Glucose Absorption in Peritoneal Dialysis: A Pilot Study

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Abstract

Background Glucose absorption in patients on peritoneal dialysis (PD) may contribute to adverse metabolic effects. Previous studies on glucose absorption were done on patients on continuous ambulatory PD, with a long dwell time. However, the growing majority of contemporary patients on PD perform automated PD with a short dwell time. Moreover, membrane characteristics and dwell time determine small-solute transport across the peritoneal membrane.

Methods In our pilot study, we used data from the peritoneal equilibration test (PET) to develop a model to estimate glucose absorption. In six randomly selected patients on PD, we calculated actual glucose absorption from directly measuring effluent glucose concentration. We then used the R programming language to create a nonlinear, least-squared regression model, inputting PET data, D2/D0, and D4/D0 to generate an exponential decay curve. This model was then used to estimate the fraction of glucose remaining in the dialysate at a particular dwell time t (Dt/D0). Daily glucose absorption was calculated by multiplying 1−Dt/D0 with the amount of glucose the patient was exposed to in 24 hours.

Results We observed the mean glucose absorption (89.7 ± 28.8 g/d), as measured from the effluent, very close to our estimate (88.12 ± 28.9 g/d), and the difference between the glucose estimation and actual absorption was not statistically significant (P > 0.05), with “W” value of 8. After validating our hypothesis, we randomly selected an independent cohort of 11 patients with ESKD who were on various PD modalities and analyzed their data. We observed that the mean daily glucose absorption of 62.7 ± 24.5 g (27.98–110.35 g), much lower than that reported in the literature, depends on dwell times and membrane characteristics in addition to the amount of glucose absorption in the cohort.

Conclusions Our model provides a simple tool for estimating glucose absorption and caloric load in contemporary patients on PD. Hopefully, the accurate estimation of caloric load and the incorporation of it into the daily caloric intake of the individual will help to reduce metabolic consequences of hyperglycemia and weight gain and improve overall outcomes of PD.

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Introduction

Patients on peritoneal dialysis (PD) are exposed to high concentrations of glucose in the dialysate, and glucose absorption may contribute to adverse metabolic effects, such as hyperglycemia, hyperlipidemia, hyperinsulinemia, and obesity. Most studies on glucose absorption have been performed on patients on continuous ambulatory PD (CAPD) with long dwell times (1,2). Grodstein et al. (1) studied glucose absorption in seven patients and concluded that glucose absorption is proportional to the amount of glucose present in PD fluid. They estimated a daily glucose absorption of 100–300 g, which amounts to approximately 400–1200 calories per day. Unlike the patients on CAPD examined in earlier studies, the growing majority of contemporary patients on PD in the United States undergo automated PD (APD) with a short dwell time (3). In 2017, 56% of all patients on PD in the United States used APD, whereas 44% of patients were on CAPD (3). Moreover, it has now become evident that, in addition to the amount of glucose exposure, membrane characteristics and dwell time determine small-solute transport across the peritoneal membrane (4). Hence, a new method of estimating glucose absorption in contemporary patients on PD is needed. In our pilot study, we used data from the peritoneal equilibration test (PET) to develop a simple model for estimating glucose absorption.

Materials and Methods

To develop a model to estimate glucose absorption in PD, we randomly selected six stable patients undergoing PD at our center (Table 1). These patients
Table 1. Glucose absorption in six patients on peritoneal dialysis

| Patient Identifier | Age (yr) | Sex | Race | PD Rx | Bag 1 Dextrose (%) | Bag 2 Dextrose (%) | Fill Volume (L) | Initial Glucose Amount (g) | Final Glucose Concentration in Effluent (mg/dl) | Effluent Volume (ml) | Glucose Absorption (g) | Direct Glucose Measurement in the Effluent | Our Model | Grodstein et al. Equation |
|--------------------|---------|-----|------|-------|-------------------|-------------------|-----------------|---------------------------|---------------------------------------------|---------------------|----------------------|------------------------------------------|------------|------------------------|
| 1                  | 65      | F   | B    | CAPD 4×2.5 L | 2.5               | 2.5               | 10              | 227                       | 690                                          | 11,600              | 146.9                 | 136.2                                     | 171.1       |                        |
| 2                  | 44      | M   | W    | NIPD 4×2.5 L | 2.5               | 2.5               | 10              | 227                       | 1167                                         | 12,341              | 84.32                 | 88.53                                     | 181.3       |                        |
| 3                  | 41      | F   | B    | NIPD 3×2 L CCPD 4×2.5 L | 2.5               | 2.5               | 6               | 136.2                     | 1134                                         | 6877                | 59.08                 | 54.48                                     | 99.6        |                        |
| 4                  | 86      | M   | W    | CCPD 4×2.5 L LF 2.5 L | 2.5               | 1.5 #BAG 3 1.5   | 12.5            | 224.6                     | 937                                          | 13,837              | 95.29                 | 88.55                                     | 114.6       |                        |
| 5                  | 67      | M   | A    | NIPD 3×2.5 L NIPD 4×2.30 L | 2.5               | 2.5               | 7.5             | 170.25                    | 1181                                         | 9129                | 62.7                  | 62.9                                     | 133.7       |                        |
| 6                  | 86      | F   | W    | NIPD 4×2.30 L | 2.5               | 2.5               | 9.20            | 208.84                    | 1235                                         | 9767                | 91.29                 | 98.1                                     | 142.59      |                        |

PD Rx, peritoneal dialysis prescription; F, female; B, Black; CAPD, continuous ambulatory peritoneal dialysis; M, male; W, White; NIPD, nocturnal intermittent peritoneal dialysis; CCPD, continuous cycler peritoneal dialysis; LF, last fill; A, Asian.

*Glucose absorption in six patients on peritoneal dialysis with actual glucose absorption as measured from effluent.

*Estimated glucose absorption using our model.

*Estimated glucose absorption using Grodstein et al.’s equation: Y=11.3x−10.9 (Y, is the glucose absorption [g/L] and x, concentration of glucose in the dialysate [g/dL/day]).
were on various PD modalities: one was on CAPD, and five patients were on APD. Medical charts were reviewed to retrieve data on their PD prescriptions, including the PD schedule, fill volumes, dwell times, and the dialysate dextrose concentration used. Additionally, PET data, including D2/D0 and D4/D0 values, were obtained. D0 is the dialysate glucose concentration (mg/dl) at the beginning of the PET study, and D2 and D4 are dialysate glucose concentrations at 2 and 4 hours of the dwell time, respectively (5). Furthermore, the glucose concentration in the pooled 24-hour dialysate effluent sample was obtained. The actual glucose absorption in a day was determined by calculating the difference between the amount of glucose instilled and that in the pooled 24-hour effluent (see Supplemental Appendix 1 for an example).

We then developed an exponential decay model on the basis of the PET data (D2/D0 and D4/D0 data) to estimate daily glucose absorption in these patients. A nonlinear, least-squared error model was created in the R programming language. Input data were taken through a user prompt that inquired upon PD diagnostic glucose absorption proportions at 2 and 4 hours (D2/D0 and D4/D0, respectively) on the basis of their PETs. The program uses least-squared residual software and runs through multiple iterations of fitting an exponential curve $y = e^{(a + bx)}$, where $y$ is the proportion of glucose in the dialysate, $x$ is the dwell time in minutes that is attached to a variable, $b$, and a noise (lurking) variable, $a$, to account for the variance of residuals (6). Once error is minimized, the new, optimized equation is used to return an estimate for the proportion of glucose ($D_t/D_0$) at the requested dwell times of interest $t$ (Figure 1). The proportion of glucose absorbed at a particular dwell time $t$ was calculated as $1 - D_t/D_0$. The total amount of glucose absorbed in a day was calculated by multiplying $1 - D_t/D_0$ with the total amount of glucose the patient was exposed to in 24 hours. Patients with multiple dwell times in their daily PD prescriptions ($t_1, t_2, t_3, etc.$) will have corresponding $D_{t1}/D_0, D_{t2}/D_0, D_{t3}/D_0$ values (see Supplemental Appendices 2 and 3 for examples). To investigate the effect of glucose concentration in the dialysate on the rate of glucose absorption, we analyzed the PET data for D2/D0 and D4/D0.

Figure 1. | Estimate for the proportion of glucose ($D_t/D_0$) at the requested dwell times of interest $t$. Patient on CCPD with five exchanges of 2.2 L and LF of 2.2 L, using 1.5% and 2.5% dextrose dialysates. Estimation of proportion of glucose absorption ($1 - D_{t1}/D_0$ and $1 - D_{t2}/D_0$) at dwell times $t_1$ (95 minutes) and $t_2$ (180 minutes). D2/D0 and D4/D0 are 0.51 and 0.35, respectively (red dots). The D2/D0 and D4/D0 values are obtained from the peritoneal equilibration test; CCPD, continuous cycler peritoneal dialysis, $D_{t1}/D_0$, ratio of glucose concentration in the dialysate at dwell time $t_1$ to that at time 0; $D_{t2}/D_0$, ratio of glucose concentration in the dialysate at dwell time $t_2$ to that at time 0; $D_{t2}/D_0$, ratio of glucose concentration in the dialysate at 2 hours to that at time 0; $D_{t4}/D_0$, ratio of glucose concentration in the dialysate at 4 hours to that at time 0; LF, last fill; $y = e^{(a + bx)}$ where $y$ is the proportion of glucose in the dialysate, $x$ is the dwell time in minutes that is attached to a variable, $b$, and a noise (lurking) variable, $a$, to account for the variance of residuals.
absorption, PET was performed in a patient using dialysates with two different concentrations of dextrose (1.5% and 2.5%).

Once our model was validated in the aforementioned six patients, we selected 11 additional patients with ESKD undergoing PD at our center to estimate glucose absorption. Medical records were reviewed to obtain clinical, demographic, and laboratory data. PD prescriptions, including PD schedules, number of exchanges, fill volumes, and dwell times for each exchange; strength of dextrose in each bag; and total fill volumes for 24 hours were recorded. PET data were retrieved, and the estimated glucose absorption was calculated using our model as mentioned previously (Figure 2).

Statistical Analyses
Mean and SD of estimated glucose absorbed was calculated in the validation and independent cohort. We have also calculated the mean and SD of estimated glucose absorption as described by Grodstein in our validation cohort to compare and contrast our results. The Wilcoxon rank sum test was used to compare the results obtained by direct measurement of glucose absorption with that estimated by our model (7). In addition, a scatter chart was plotted using the values of direct glucose absorption versus those estimated by our model (Figure 3).

The study was approved by the institutional review board of the University of Texas Southwestern Medical Center.

Results
Six patients on various PD prescriptions were included in our validation study. Demographic and other clinical data are shown in Table 1. We observed that the estimation of glucose with our model (mean, 88.12±28.9 g/d) was very similar to the actual glucose absorption (mean, 89.78±28.8 g/d) as measured from effluent (Figure 3). The difference between the glucose estimation and actual absorption was not statistically significant (P>0.05), with "W" value of 8. We also estimated glucose absorption on the basis of the linear regression equation Y=11.3x–10.9, where Y is the glucose absorption (g/L) and x is the concentration of glucose in the dialysate (g/dl per day), as described by Grodstein et al. (1). In contrast to our model, the equation described by Grodstein et al. grossly overestimated glucose absorption (mean, 140.48±28.8 g/d).

Once our results were validated in six patients, we selected 11 additional patients to estimate glucose absorption using our model. Clinical characteristics and demographics of the 11 patients are outlined in Table 2. Patients were on PD for a period of 1–7 years. Seven patients used dialysis bags with a single dextrose concentration, whereas the remaining patients used bags with different dextrose concentrations. Dwell times on the cycler ranged from 80 to 105 minutes, whereas the times on manual exchanges ranged from 3 to 4 hours. The average total daily glucose exposure was 156.9±41.75 g, and ranged from 108.8 to

Table 2. Patient characteristics

| Patient Characteristics at PD Initiation | Value |
|-----------------------------------------|-------|
| Age (yr), mean (SD)                     | 54±24.0|
| Sex male/female, n                      | 7/4   |
| Ethnicity, n (%)                        |       |
| Black                                   | 6 (55) |
| Hispanic                                | 5 (45) |
| Cause of renal failure, n (%)           |       |
| Diabetes and hypertension               | 5 (45) |
| Hypertension                            | 4 (36) |
| Sickle cell disease                     | 1 (9)  |
| Lupus                                   | 1 (9)  |
| Years on peritoneal dialysis, range     | 1–7 yr |
| PD prescription, n (%)                  |       |
| NIPD                                    | 6 (55) |
| CCPD                                    | 4 (36) |
| CAPD                                    | 1 (9)  |

PD, peritoneal dialysis; NIPD, nocturnal intermittent PD; CCPD, continuous cycler-assisted PD; CAPD, continuous ambulatory PD.
Table 3. Estimation of glucose absorption in the independent cohort of 11 patients on peritoneal dialysis

| Patient Identifier | D2/D0 | D4/D0 | t1 (h: min) | D1/ D0 | t2 (h) | D2/D0 | t3 (h) | D3/D0 | t4 (h) | D4/D0 | PD Rx | Bag 1 Dextrose (%) | Bag 2 Dextrose (%) | MDE (%) | Glucose Exposure (g) | Glucose Absorbed (g) |
|-------------------|------|------|-------------|------|------|------|------|------|------|------|------|------|----------------|----------------|--------|------------------|------------------|
| 7                 | 0.46 | 0.14 | 1:45        | 0.47438 | 3:00 | 0.27706 |       |       |       |       |       | CCPD 4×2 L, LF 2 | 1.5             | 1.5    | 136              | 76.85            |
| 8                 | 0.57 | 0.43 | 1:30        | 0.6958  |      |       |       |       |       |       |       | NIPD 4×2 L        | 1.5             | 1.5    | 108.8            | 33.1             |
| 9                 | 0.51 | 0.31 | 1:30        | 0.62394 |      |       |       |       |       |       |       | NIPD 4×2 L        | 2.5             | 2.5    | 181.6            | 68.29            |
| 10                | 0.58 | 0.43 | 1:45        | 0.66088 |      |       |       |       |       |       |       | NIPD 4×2.2 L      | 1.5             | 1.5    | 119.68           | 40.59            |
| 11                | 0.43 | 0.28 | 1:20        | 0.6086  |      |       |       |       |       |       |       | NIPD 4×2.5 L      | 1.5             | 2.5    | 172.4            | 67.47            |
| 12                | 0.54 | 0.37 | 1:25        | 0.6788  |      |       |       |       |       |       |       | NIPD 4×2.5 L      | 2.5             | 1.5    | 190.6            | 61.78            |
| 13                | 0.56 | 0.47 | 1:30        | 0.7066  |      |       |       |       |       |       |       | NIPD 4×2 L        | 2.5             | 2.5    | 181.6            | 53.28            |
| 14                | 0.68 | 0.51 | 1:40        | 0.74286 |      |       |       |       |       |       |       | NIPD 4×2 L        | 1.5             | 1.5    | 108.8            | 27.98            |
| 15                | 0.37 | 0.39 | 1:40        | 0.6531  | 3:00 | 0.468  |       |       |       |       |       | CCPD 4×2 L        | 1.5             | 1.5    | 136              | 52.21            |
| 16                | 0.51 | 0.35 | 1:35        | 0.6429  | 3:00 | 0.4149 |       |       |       |       |       | MDE 2L            | 1.5             | 2.5    | 245.29           | 98.89            |
| 17                | 0.42 | 0.24 | 4:00        | 0.24    | 4:00 | 0.24   | 4:00 | 0.24 | 4:00 | 0.24 |       | CAPD 5×2 L        | 2.5             |        | 145.2            | 110.35           |

D2/D0, ratio of glucose concentration in the dialysate at 2 h to that at time 0; D4/D0, ratio of glucose concentration in the dialysate at 4 h to that at time 0; t1, dwell time 1; D1/D0, ratio of glucose concentration in the dialysate at dwell time t1 to that at time 0; t2, dwell time 2; D2/D0, ratio of glucose concentration in the dialysate at dwell time t2 to that at time 0; t3, dwell time 3; D3/D0, ratio of glucose concentration in the dialysate at dwell time t3 to that at time 0; t4, dwell time 4; D4/D0, ratio of glucose concentration in the dialysate at dwell time t4 to that at time 0; PD Rx, peritoneal dialysis prescription; MDE, midday exchange; CCPD, continuous cycler peritoneal dialysis; LF, last fill; NIPD, nocturnal intermittent peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.
245.29 g. The mean daily glucose absorption was 62.7±24.5 g (range, 27.98–110.35 g), as outlined in Table 3. The corresponding average daily calories were 223.4±78.1 and ranged from 107.23 to 312.02 in patients on APD. The patient on CAPD had a daily caloric load of 424.85 kcal/g. For calories derived from the absorption of glucose, we used the value of 3.85 kcal/g of anhydrous dextrose absorbed (8).

To determine whether or not different glucose concentrations in the dialysate affects the rate of glucose absorption, PET was performed in a patient using dialysates with two different dextrose concentrations of 1.5% and 2.5%. The data from the two studies were found to be nearly identical (Figure 4).

Further analysis of our data showed that amount of glucose absorption depends on the amount of glucose exposure in many patients (patient identifier [ID] 7, 8, 9, 10, and 11) (Table 3). However, in some instances, patients with lower glucose exposure (ID 17) had higher glucose absorption compared with patients with a higher glucose exposure (ID 16) (Table 3). On the other hand, some patients with similar glucose exposures (140.6±4 g) and similar membrane characteristics (ID 17 and 7) had different amounts of glucose absorption (110.35 and 76.85 g, respectively), largely due to different dwell times (Table 3). Finally, two patients, ID 9 and ID 13, had a similar glucose exposure (181.6 g) and similar dwell times (90 minutes) but had different glucose absorption (68.29 versus 53.28 g, respectively) due to different membrane-transport characteristics. By the same token, a lower membrane-transport status of our patient on CAPD (case 1, Table 1) likely led to overestimation of glucose absorption by Grodstein et al.’s linear-regression equation when compared with estimation using our model.

Discussion

Conventional PD solutions contain glucose as the osmotic agent to provide ultrafiltration. However, various quantities of glucose are absorbed from the dialysate into the bloodstream. Although it provides a source of energy, glucose absorption can be associated with dire metabolic consequences and accompanying adverse cardiovascular outcomes (9). Due to logistic constraints, it is quite cumbersome to directly measure glucose absorption during PD. Concomitantly, limited data are available on estimation of glucose absorption in contemporary patients on PD. Grodstein et al. studied peritoneal absorption in seven patients on CAPD with a long and fixed dwell time, using 1.5% and 4.25% dextrose dialysate solutions, and observed a large amount of daily glucose absorption (182±61 g) during CAPD (1). They observed a high correlation between the amount of glucose absorbed and the average concentration of glucose in the dialysate, and predicted that glucose absorption in patients on CAPD with a long and fixed dwell time solely depends on one variable: the amount of glucose in the dialysate. However, it is now evident that, in addition to the toxicity of the dialysate, glucose absorption also depends on peritoneal membrane-transport characteristics and dwell time (4,10). Heimburger et al. (4) studied the diffusion mass transport properties of small solutes, including glucose, in 41 patients on CAPD (four exchanges of 2 L, 6-hour dwell) using conventional dextrose dialysate solutions, and showed that glucose absorption during the PD dwell time is exponential and the fractional absorption of glucose in a patient is similar to the different tonicities of the dialysate. Similar results were found in our study. On performing PET using two different dextrose concentrations (1.5% and 2.5%), the percentage absorption of glucose over time was nearly identical using both solutions (Figure 4). Heimburger et al. further observed that, on average, 75% of the initial intraperitoneal glucose amount is absorbed by the end of 6 hours, with 50% of glucose being absorbed in the first 90 minutes. Additionally, they noted, by direct measurement, that the total amount of daily glucose absorption ranged from 80 to 220 g in patients on CAPD, depending on the concentration of glucose in the dialysate (4).

In contrast to the aforementioned studies, contemporary patients use nighttime cyclers with short and variable dwell times. Moreover, unlike patients on CAPD, many patients...
on cyclers use dialysate bags with different tonicities that allow admixture of dialysate solutions with different glucose concentrations. Hence, a novel method to estimate glucose absorption in contemporary patients on PD is needed.

In our pilot study, we developed an exponential decay model using PET data to estimate glucose absorption in patients on PD. It accurately estimated glucose absorption, in contrast to the model used by Grodstein et al. that predictably overestimated the glucose absorption in our patients, who mainly used cyclers with short and variable dwell times. Although, in concurrence with Grodstein et al. (1), several patients showed correlation between glucose absorption and the amount of glucose in the dialysate, there were instances when patients with a higher glucose exposure actually had lower glucose absorptions, despite similar dwell times, likely due to differences in membrane-transport characteristics (Table 3). Likewise, we also observed the reverse situation, where some patients with a lower glucose exposure than others had higher glucose absorption, mainly due to longer dwell times or differences in membrane-transport characteristics (Table 3). Overall, the daily amount of glucose absorption and the consequent caloric load was much lower in our patients compared with what was observed in earlier studies, which were done on patients on CAPD (1,4,11,12). The lower glucose absorption in contemporary patients on PD using a cycler is likely because of lower dwell times and the avoidance of 4.25% dextrose dialysate solutions.

Our study provides a simple tool for estimating glucose absorption and caloric load in contemporary patients on PD, and takes into consideration factors (including membrane transport characteristics, dwell time, and glucose exposure) that play an important role in glucose absorption. Although direct measurement of glucose from the effluent is the most accurate way to measure glucose absorption, this method is cumbersome and has logistic constraints. Glucose is not routinely measured in the effluent during quarterly Kt/V estimations, and requires a separate order set. Moreover, patients may use dialysate bags with different tonicities on their daily PD schedules. Additionally, patients on APD often connect dialysate bags of different tonicities in variable orders to the cyclers on a day-to-day basis. Hence, direct measurement of effluent glucose would require multiple collections of the effluents, reflecting the corresponding combinations and sequences of bags used. Our model obviates such need and is able to estimate glucose absorption in all ensuing settings. Our study is limited by its small size. We plan to extend the study to include our entire cohort of >150 patients. In addition, we plan to develop website-based and smart phone applications for easy use by physicians, advanced practice providers, dietitians, and, eventually, patients. Hopefully, the accurate estimation of caloric load and the incorporation of it into the daily caloric intake of the individual will help to reduce metabolic consequences of hyperglycemia, hyperlipidemia, and weight gain (13,14) and improve overall outcomes of PD.

Disclosures
All authors have nothing to disclose.

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Author Contributions
S. Kotla was responsible for data curation and reviewed and edited the manuscript; S. Kotla, A. Saxena, and R. Saxena were responsible for methodology; S. Kotla and R. Saxena conceptualized the study, were responsible for formal analysis and funding acquisition, and wrote the original draft; and A. Saxena was responsible for software.

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