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CLINICAL STUDY

Solutes Transport Characteristics in Peritoneal Dialysis: Variations in Glucose and Insulin Serum Levels

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Background. Differences in small solutes transport rate (SSTR) during peritoneal dialysis (PD) may affect water and solutes removal. Patients with high SSTR must rely on shorter dwell times and increased dialysate glucose concentrations to keep fluid balance. Glucose absorption during peritoneal dialysis (PD), besides affecting glucose and insulin metabolism, may induce weight gain. The study aimed at examining acute glucose and insulin serum level changes and other potential relationships in PD patients with diverse SSTR. *Methods*. This cross-sectional study used a modified peritoneal equilibration test (PET) that enrolled 34 prevalent PD patients. Zero, 15, 30, 60, 120, 180, and 240-minute glucose and insulin serum levels were measured. Insulin resistance index was assessed by the homeostasis model assessment (HOMA-IR) formula. SSTR categories were classified by quartiles of the four-hour dialysate/serum creatinine ratio (D_4/P_{Cr}). Demographic and clinical variables were evaluated, and the body mass index (BMI) was estimated. Correlations among variables of interest and categories of SSTR were explored. *Results*. Glucose serum levels were significantly different at 15, 30, and 60 minutes between high and low SSTR categories (p = 0.014, 0.009, and 0.022). Increased BMI (25.5 ± 5.1) and insulin resistance [HOMA-IR = 2.60 (1.40–4.23)] were evidenced overall. Very strong to moderate correlations between insulin levels along the PET and HOMA-IR (r = 0.973, 0.834, 0.766, 0.728, 0.843, 0.857, 0.882) and BMI (r = 0.562, 0.459, 0.417, 0.370, 0.508, 0.514, 0.483) were disclosed. *Conclusions*. Early glucose serum levels were associated with SSTR during a PET. Overweight or obesity and insulin resistance were prevalent. An association between insulin serum levels and BMI was demonstrated.

Keywords end-stage renal disease, insulin resistance, obesity, renal dialysis, solutes transport

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INTRODUCTION

Ultrafiltration in peritoneal dialysis (PD) has been usually induced by using high glucose dialysate concentrations. However, a significant fraction of the peritoneal glucose is absorbed, adding an extra load to ingested calories.[1,2] Patients on PD may gain weight and, not infrequently, become obese.[3] At a particularly higher risk are females and individuals with non-insulin-dependent diabetes, or prior obesity. Insulin resistance (IR) is knowingly prevalent among obese individuals, non-insulin-dependent diabetes, and end-stage renal disease (ESRD) patients.[4] The occurrence of IR, irrespective of cause, has been associated with lipid abnormalities.[5] PD patients often present dyslipidemia, mostly hypertriglyceridemia.[6] Evidence suggests that triglycerides levels are related with the peritoneal glucose load.[7]

Patients initiating PD demonstrate diverse small solutes transport rate (SSTR) that may significantly change along treatment.[8,9] Knowledge of the SSTR allows for better individual fluid and solutes balance; several clinical tests have been used to evaluate the SSTR. The most commonly used one—the peritoneal equilibration test (PET)—computes a four-hour dwell time peritoneum to a two-hour serum creatinine ratio, and classifies the peritoneal transport as high, high-average, low-average or low.[10]

High SSTR patients consistently use more concentrated glucose dialysis solutions in addition to shorter dwell times to achieve adequate fluid drainage and to keep water and salt balance, thus possibly increasing glucose absorption. Previous evidence has shown that serum insulin levels and peritoneal glucose loads are closely related.[4] Yet glucose absorbed from the peritoneal cavity led to delayed increments in insulin serum levels when compared with similar ingested loads.[1]

Recent evidence suggests that patients on CAPD, with high SSTR, are at increased risk of death.[11] The relationship between peritoneal SSTR and changes in glucose or

insulin serum levels during a PD cycle may add information to better understand morbidity and mortality in peritoneal dialysis. The study aimed at evaluating changes in insulin and glucose serum levels during a PET, the occurrence of IR, and correlating variables of interest in stable patients on PD with diverse SSTR.

METHODS

The study enrolled 34 volunteer, stable, non-diabetic patients undergoing PD longer than one month and free of peritonitis for more than three months. The research protocol was approved by the hospital Research Ethics Committee, and all patients gave an informed consent before inclusion.

All subjects were evaluated in early morning, following a day of 1.5% glucose dialysis solution exchanges (the last one at 11:00 pm). The participants underwent a modified (two-liter, 4.25% glucose solution infusion) PET procedure[12] according to the original technique[10] to enhance glucose and insulin serum levels during the test period. The peritoneal transport category was determined by the four-hour dialysate/serum creatinine ratio (D_4/P_{Cr}) as low, low-average, high-average, and high, either following a standardized grading approach or using quartiles of the study population observed ratios.[10,13] Categories demarcation by quartiles produced a more uniform distribution, contrary to the original procedure that necessarily allocates fewer subjects to the external (high and low) transport categories.

The homeostasis model assessment (HOMA-IR) was employed to calculate the insulin resistance index.[14] HOMA-IR relates serum glucose and insulin levels using the following formula:

$$\text{fasting serum insulin } (\mu\text{IU/mL}) \times \text{fasting serum glucose } (\mu\text{mol/L}) / 22.5.$$

It has been shown that log-transformed HOMA-IR (HOMA-IR-log) strongly correlates with the more complex and time-consuming euglycemic insulin clamp, the gold standard in appraisal of the insulin resistance index.[15]

The following variable groups were examined:

- *Demographic*. Age, gender, height, weight, and race;
- *Clinical and therapeutic.* Blood pressure, cause of ESRD, modality of PD (continuous or automated), number of episodes of peritonitis, time on dialysis or PD, and residual urine volume; and
- *Laboratory*. Serum glucose at 0, 15, 30, 60, 120, 180, and 240 minutes; serum insulin at 0, 15, 30, 60, 120, 180, and 240 minutes; serum creatinine at 120 minutes (P_{Cr}); dialysate creatinine at 120 and 240 minutes (D_4).

Non-deproteinized automated Jaffé reaction (with correction for high glucose concentrations) and a kinetic glucose-oxidase automated method were used in creatinine and glucose estimations, respectively (Advia 1650, Bayer Healthcare, Tarrytown, New York, USA). A chemiluminescence procedure (Immulite 2000, Diagnostic Products, Los Angeles, California, USA) was employed in insulin determinations.

Categorical variables are presented as frequency and percentage, continuous variables as mean ± standard deviation or median and inter-quartile range. Either chi-square (χ^2) or Fisher's exact test was employed to compare categorical variables. Either a one-way ANOVA (with post-hoc Tukey) or Kluskal-Wallis test was used to compare continuous variables. Pearson or Spearman's correlation coefficients were used to evaluate associations and tendencies. In all comparisons, a value of $p \leq 0.05$ was considered significant. A Statistical Package for Social Sciences (SPSS, version 11.5 for Windows, SPSS Inc, Chicago, Illinoise, USA) was used in all statistical analyses.

RESULTS

Twenty of the 34 enrolled patients had never presented peritonitis, and, in the remaining patients, the shortest interval between a peritonitis episode and the current SSTR evaluation was three months. Mean age and gender distribution were similar to previous series, and a majority of patients was Caucasian. The most frequent diagnoses associated with ESRD were hypertension and polycystic kidney disease. With regard to modality of PD, most patients had been on continuous ambulatory peritoneal dialysis (CAPD) and were stable for a considerable time. Blood pressure was under adequate control, overall, and in 40% of the subjects, the mean BMI was above normal (32% overweight and 18% obese). Relevant demographic and clinical data are shown in Table 1.

Limits of the SSTR categories, stratified by the standard procedure or by quartiles of the D_4/P_{Cr} distribution, are depicted in Table 2.

Overall fasting glucose and insulin levels were 5.11 ± 0.94 mmol/L and 79.0 (54.5–141.6) pmol/L, respectively. Fasting glucose (5.27 ± 0.83, 4.94 ± 1.28, 5.38 ± 0.83, 4.83 ± 0.67 mmol/L; $p = 0.55$) and insulin (70.0 [45.8–193.4], 67.8 [44.4–86.8], 109.7 [68.2–149.4], 106.1 [47.1–175.0] pmol/L; $p = 0.828$) serum levels for high, high-average, low-average, or low categories, respectively,

Table 1
Demographic and clinical characteristics (n = 34)

Parameter	Value
Age (years), mean ± SD	52.6 ± 13.6
Female (%)	19 (56)
Caucasian (%)	32 (94)
Cause of ESRD (%)	
Glomerulopathy	3 (9)
Polycystic kidney disease	12 (35)
Hypertension-related	14 (41)
Systemic lupus erythematosus	1 (3)
Other	4 (12)
Time on PD (months), median (IQR)	19.5 (5.0–30.3)
Residual diuresis (ml), median (IQR)	500 (160–1000)
Modality of PD (%)	
CAPD	25 (73)
APD	9 (27)
DBP (mm Hg), mean ± SD	80 ± 13
SBP (mm Hg), mean ± SD	128 ± 21
BMI, mean ± SD	25.5 ± 5.1
Height (m), mean ± SD	1.65 ± 0.09
Weight (kg), mean ± SD	69.6 ± 15.8

Abbreviations: SD = standard deviation, ESRD = end-stage renal disease, IQR = inter-quartile range, PD = peritoneal dialysis, CAPD = continuous ambulatory peritoneal dialysis, APD = automated peritoneal dialysis, DBP = diastolic blood pressure, SBP = systolic blood pressure, BMI = body mass index.

Table 2
SSTR categories by the standard method and quartiles of D_4/P_{Cr} (n = 34)

Category	Standard*	n	Quartiles	n
High	≥0.84–0.98	6	≥0.81–0.98	8
High-average	≥0.72–<0.84	9	≥0.70–<0.81	9
Low-average	≥0.59–<0.72	16	≥0.63–<0.70	8
Low	0.39–<0.59	3	0.39–<0.63	9

*according to Twardowski et al.[10]

Abbreviations: SSTR = small solutes transport rate, D_4/P_{Cr} = four-hour peritoneal/two–hour plasma creatinine ratio.

were not significantly different. HOMA-IR suggested some degree of insulin resistance, both overall (2.60 [1.4–4.23]) and for each category (2.24 [1.31–5.50]; 2.34 [1.06–2.94]; 3.41 [2.10–5.61]; 3.01 [1.33–6.31]) of SSTR (from high to low), with no significant differences among categories.

Glucose serum levels were significantly different (p = 0.014, 0.009, and 0.022, respectively) only at the 15-, 30-, and 60-minute measurements, and between categories high and low (8.10 ± 2.16, 9.16 ± 2.72, 8.94 ± 2.89 vs. 5.77 ± 0.89, 6.33 ± 0.94, 6.27 ± 1.17, respectively). Glucose serum levels by category of peritoneal transport along the PET are shown in Figure 1. No significant differences were demonstrated for simultaneous insulin serum concentrations among transport categories.

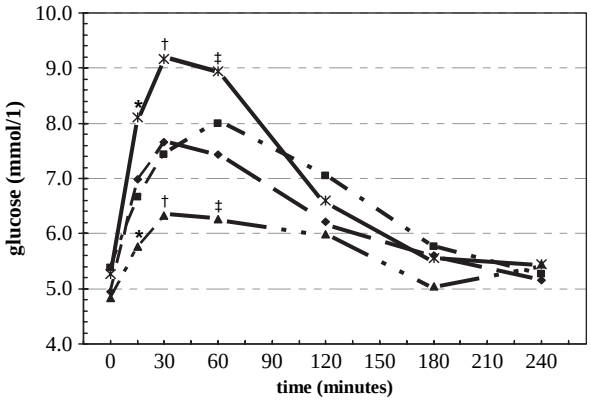

Figure 1. Glucose mean serum level for each category of SSTR during a PET: —, high; ---, high-average; – · -, low-average; – · ·, low peritoneal transport, respectively; ANOVA with post-hoc Tukey. *Significantly different at 15-, 30-, and 60-minute measurements (p = 0.014; p = 0.009; p = 0.022, respectively).

Glucose serum levels at 15-, 30-, and 60-minute intervals strongly to moderately correlated with D_4/P_{Cr} (r = 0.535, p = 0.001; r = 0.529, p = 0.001; r = 0.406, p = 0.008, respectively). No significant association was found between insulin serum level and D_4/P_{Cr}. HOMA-IR-log strongly correlated with BMI (r=0.517, p = 0.002) at 0, 15, 30, 60, 120, 180, and 240 minutes. BMI also moderately to strongly correlated with insulin levels (r = 0.562, p = 0.001; r = 0.459, p = 0.007; r = 0.417, p = 0.016; r = 0.370, p = 0.034; r = 0.508, p = 0.002; r = 0.514, p = 0.002; r = 0.483, p = 0.004) at 0, 15, 30, 60, 120, 180, and 240 minutes, respectively.

DISCUSSION

The study revealed a high prevalence of insulin resistance, overweight, or obesity among patients with ESRD undergoing PD. During the PET, early glucose serum levels were significantly different only between high and low categories of SSTR, and moderately correlated with D_4/P_{Cr}. Also, positive correlations among BMI, glucose, and insulin serum levels were found at all evaluated intervals. Predominantly Caucasian subjects undergoing PD—mostly CAPD—for a considerably long time, and with mean age comparable to that of other series, comprised the current study population.[16] All retained some residual renal

function (as estimated by daily urine output) and maintained adequate blood pressure control.

D_4/P_{Cr} mean and median values were comparable to those found in several previous studies.[10,16,17] The standard classification of SSTR uses a particular study population mean D_4/P_{Cr} value, plus one and two standard-deviations above and below the mean, to classify the peritoneal transport as high, high-average, low-average, or low.[10] However, its use in the current study unevenly allocated a majority of subjects to the central categories (9 to high-average, and 16 to low-average), with very few remaining in the external categories. Classifying by quartiles of D_4/P_{Cr} corrected for that problem without unduly changing the categories limit values.[13] Nine patients were removed from median-low (three to high-average, and six to low) category, and two additional subjects were reallocated from high-average to high category.

Mean fasting glucose and insulin levels were comparable to those of previous studies.[18–20] Additionally, the study validated previous observations on the occurrence of insulin resistance in stable, non-diabetic ESRD patients. (Of note, a recent epidemiological study found a median HOMA-IR value of 2.1 in non-diabetic young Caucasian individuals.[19,21,22]) When examined by category of SSTR, the HOMA-IR was higher in median-low and low SSTR categories, suggesting that the degree of IR was not associated with SSTR and possibly dependent on the presence of ESRD, or on different weight increments along the dialysis treatment. The early glucose levels difference between categories high and low, as well as a positive correlation between early glucose levels and D_4/P_{Cr}—unassociated with significant differences in the corresponding insulin levels—suggest that SSTR may account for the discrepancies.

HOMA-IR-log and BMI strong to moderate correlations with insulin levels at all selected intervals of the PET suggest increasing insulin secretion in response to the absorbed glucose loads. Furthermore, a strong correlation between HOMA-IR and BMI, found in previous series, suggests that weight gain and IR may have developed along the dialysis treatment.[23,24] However, a correlation between HOMA-IR-log, or BMI, and time on PD was not evidenced. Obesity and IR have been associated with cardiovascular risk factors (i.e., hypertension and dyslipidemia).[6,25] Dyslipidemia, especially hypertriglyceridemia, is a common event in patients on PD.[5] Additionally, patients on CAPD with high peritoneal SSTR seem to be at increased cardiovascular risk.[11] One could speculate that PD patients with high SSTR gain more weight, become progressively insulin-resistant, and develop dyslipidemia. However, the current results do not support such a chain of events. If dependent on peritoneal SSTR, early serum glucose and insulin levels should have progressively reached higher values, from low to high category. Yet a significant difference was evident only between the external categories. However, it cannot be ruled out that by expanding the study population, separation among categories would appear. Alternatively, classifying SSTR in four categories may be arbitrary, artificial, or unnecessary—only extreme variations in transport may be functionally significant. Additionally, the concept of peritoneal SSTR involves more than simply membrane channel permeability characteristics to include differences in microcirculation and surface area as well,[26,27] making data interpretation considerably more complex. No correlations among D_4/P_{Cr}, transport categories and HOMA-IR or HOMA-IR-log were found, suggesting that insulin resistance developed in presence of ESRD and independently of peritoneal transport characteristics.

The study had some limitations, though. First, it can be argued that the number of enrolled patients was not large enough to allocate a suitable number of participants to categories high and low by the standard classification, used in most studies. However, classifying by quartiles of D_4/P_{Cr} transferred subjects from category median-low to low, and added two participants to category high from high-average. Additionally, category limits in both classifications were rather similar. If any, the new distribution anticipated effect would be reducing early mean glucose and insulin levels on the external categories. Yet significant differences were only demonstrated between those categories. Second, HOMA-IR was used to assess the insulin resistance index, instead of the standard glucose clamp. Previous studies have demonstrated an excellent correlation between both tests in normal individuals, in non-insulin dependent diabetes, and in ESRD patients. Furthermore, HOMA-IR has been validated as a reliable tool in estimating the insulin resistance index in several conditions, including ESRD patients.[15,28] Third, this was a cross-sectional study, and longitudinal variations in weight were not examined. Thus, it cannot be ruled out that patients in the lower transport categories were heavier and more insulin-resistant when starting renal function replacement therapy.

In summary, during a PET, only early glucose serum levels of patients allocated to the external SSTR categories significantly differed. Positive correlations of glucose serum levels and SSTR possibly reflect membrane transport characteristics. A significant fraction of PD patients was overweight or obese, displaying variable degrees of IR independently of peritoneal transport characteristics. The possible associations of SSTR with changes in glucose and insulin metabolism and cardiovascular morbidity and mortality in CAPD must be further addressed.

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