Peritoneal Transport Properties and Dialysis Dose Affect Growth and Nutritional Status in Children on Chronic Peritoneal Dialysis

FRANZ SCHAEFER,* GÜNTERT KLAUS,† OTTO MEHLS,* and THE MID-EUROPEAN PEDIATRIC PERITONEAL DIALYSIS STUDY GROUP†
*Pediatric Nephrology Division, University Children’s Hospital, Heidelberg, Germany; and †Pediatric Nephrology Division, University Children’s Hospital, Marburg, Germany.

Abstract. To evaluate possible effects of peritoneal transport and dialysis dose on the physical development of children on chronic peritoneal dialysis, a cohort of 51 children was prospectively followed for 18 mo. Peritoneal transport characteristics were assessed by serial peritoneal equilibration tests (PET), dialysis efficacy by dialysate and residual renal clearance measurements, and growth and nutritional status by the longitudinal changes (Δ) of height SD score (SDS), body mass index (BMI) SDS, and serum albumin. Δ height SDS was negatively correlated with the creatinine equilibration rate observed in the initial PET (r = −0.31, P < 0.05). Multiple regression analysis confirmed the negative effect of the high transporter state (partial r² = 0.07), and disclosed an additional positive effect of dialytic C Cr (partial r² = 0.11) and a weak negative effect of daily dialysate volume (partial r² = 0.04) on Δ height SDS. Δ BMI SDS was strongly age-dependent (r = −0.48, P < 0.001); while relative body mass gradually increased below 4 yr of age, it remained stable in older children. Positive changes in BMI SDS were associated with rapid PET creatinine equilibration rates (univariate r = 0.35, P < 0.05) and/or large dialysate volumes (multivariate partial r² = 0.11), suggesting a role of dialytic glucose uptake in the development of obesity. The change in serum albumin concentrations was positively correlated with dialysate volume (partial r² = 0.14), and negatively affected by dialytic protein losses (partial r² = 0.06). In conclusion, the peritoneal transporter state is a weak but significant determinant of growth and body mass gain in children on chronic peritoneal dialysis. Rapid small solute equilibration contributes to impaired growth but enhanced acquisition of body mass. Dialytic small solute clearance has a weak positive effect on statural growth independent of the transporter state, but does not affect body mass gain.

In adult patients on chronic peritoneal dialysis (CPD), evidence is increasing that treatment outcome is strongly associated with the efficacy of blood purification (1–7). The daily clearances of creatinine and urea are inversely related to morbidity and mortality rates, and evidence-based guidelines for target clearances of these markers in CPD patients have recently been outlined (8). Moreover, the peritoneal membrane transport properties independently affect outcome in adult CPD patients (9–11).

PD prescriptions in children are still largely empirical, and mainly aimed at optimizing daily ultrafiltration and limiting blood urea nitrogen levels to a range that precludes overt signs of uremic toxicity. Peritoneal transport capacity assessments and regular clearance measurements are performed only in a small minority of pediatric dialysis centers. Reasons for the limited interest in efficacy questions in pediatric PD are the generally low morbidity and mortality rates and the relatively short average dialysis periods of children. These factors, together with the small patient numbers in each pediatric dialysis center, render an assessment of PD adequacy in children difficult. Nonetheless, we believe that important possible end points of treatment outcome can be examined in children, which include statural growth, nutritional parameters, and physical and cognitive performance.

In an attempt to evaluate possible effects of individual peritoneal transport properties and delivered PD clearances on the course of growth and nutritional indices, we prospectively followed, in a multicenter effort, 51 children who remained on CPD treatment for 18 mo. The patients were continuously monitored with respect to their anthropometric development, peritoneal transport characteristics, delivered dialysis clearances, and residual renal function.

Materials and Methods

Patients

Between June 1993 and January 1997, 213 children and adolescents with end-stage renal failure on CPD in 16 Mid-European pediatric dialysis centers were enrolled in a prospective study designed to evaluate possible relationships between peritoneal transport characteristics, residual and dialysate clearances, and treatment outcome as judged by the evolution of growth and nutritional parameters. Of the 213 original patients, 42 late pubertal adolescents were excluded from
this analysis because of insufficient residual growth potential. Ninety-nine of the remaining 171 patients (58%) were transplanted within the 18-mo observation period. Five patients died due to causes not directly related to renal failure (liver failure, fulminant infection, car accident). In two patients, PD was terminated because of partial recovery of renal function, and two cases were lost to follow-up because of a change of the dialysis center. Transfer to hemodialysis due to "technique failure" was required in 12 patients (7%). Fifty-one pre- or early pubertal children completed a follow-up period of 18 mo under continued CPD treatment; their results are reported here.

Twenty-six boys with a median age of 8.0 (range, 0.1 to 15.7) y; 25 girls with a median age of 9.1 (range, 0.8 to 13.0) y were studied. Underlying renal disorders included renal hypo-/dysplasia (n = 13), obstructive uropathy (n = 3), nephronophthisis (n = 3), focal segmental glomerulosclerosis (n = 5), membranoproliferative glomerulonephritis (n = 3), hemolytic uremic syndrome (n = 3), nephropathic cystinosis (n = 3), diffuse mesangial sclerosis (n = 2), congenital nephrotic syndrome (n = 2), epimembranous glomerulonephritis (n = 1), postasphatic (n = 2) or thrombotic (n = 2) perinatal renal failure, Schönlein-Henoch purpura (n = 1), Alport syndrome (n = 1), nephrocalcinosis (n = 1), chronic interstitial nephritis (n = 1), and unknown (n = 5).

Median duration of dialysis at time of enrollment was 4.4 (range, 0 to 72) mo; 14 patients were enrolled at start of PD. Eight patients received recombinant human growth hormone (rhGH) at study entry, and in another 11 patients rhGH treatment was started within the observation period. All patients received erythropoietin and iron substitution. Vitamin D, phosphate binders, sodium bicarbonate, and antihypertensive medication were given according to clinical needs.

At the start of the study, 21 patients were on continuous ambulatory PD (CAPD) and 30 were on automated PD (APD). The APD patients usually instilled only a small amount of dialysis fluid (25 to 50% of normal fill volume) during daytime. Forty percent of the children were anuric.

**Study Protocol**

At study entry and every 6 mo thereafter, a standardized pediatric peritoneal equilibration test (PET) and a 24-h dialysate and urine collection were performed on an outpatient basis. If an episode of peritonitis occurred shortly before an examination date, the PET was delayed by at least 4 wk. The patient’s anthropometric status, serum albumin level, and the current dialysis prescription were recorded every 3 mo. Fifteen percent of the anticipated PET and clearance examinations were missed due to intercurrent clinical or organizational problems. The individual PD prescription was left entirely to the physician in charge of the child; no general prescription guidelines were made.

**Assessments**

Parents were instructed to record the precise sampling intervals and volumes of the collected dialysate and urine, and to bring the complete urine and either the total drained dialysate or, in older children, a 50-ml sample of the thoroughly mixed total dialysate. The PET was performed according to a previously published protocol (12). Briefly, a standardized volume of 1000 ml/m² body surface area of a 2.27% glucose solution was instilled. Ten percent of the instilled volume was drained after 5, 30, 60, 120, and 180 min, and reinstilled after withdrawing 5 ml of dialysate for analysis. A final 5-ml sample was obtained after complete drainage at 240 min. At each time point, 5 ml of the drained dialysate was withdrawn for further analysis. A single blood sample was obtained after 120 min.

Height (to the nearest mm) and weight (to the nearest 0.1 kg) were measured according to standardized international guidelines (13). The height measurements were made by the same observer whenever possible to reduce interobserver variability.

**Laboratory Measurements**

All samples were kept frozen at −20°C until assaying. All laboratory analyses were performed centrally at the laboratory of Heidelberg University Children’s Hospital. Creatinine, glucose, and urea were measured in each blood and dialysate sample, and albumin and β₂-microglobulin in blood and in the 24-h dialysate collections. In the urine, creatinine and urea were measured. Creatinine was determined using the modified Jaffe reaction with correction of dialysate creatinine measurements for assay interference by dialysate glucose, as described previously (12). Blood and dialysate glucose and urea were measured by enzyme assays. Albumin and β₂-microglobulin were measured using turbidimetric assays on a Behring autoanalyzer (Marburg, Germany).

**Calculations**

Residual GFR was estimated by the mean of the urinary creatinine and urea clearances standardized to 1.73 m² body surface area. The total CCr, was calculated as the sum of dialysate C, and residual GFR. Daily dialysate and total Kt/V of urea was calculated as the ratio of 24-h dialysate (= urinary) urea clearance divided by total body water (TBW, liters). TBW was estimated from height and weight using the child-specific equations of Cheek et al. (14). The protein equivalent of nitrogen appearance (PNA) was calculated using the pediatric adaptation of the Borah formula (15) proposed by Harmon et al. (16).

Integrated mean values of serum albumin, weekly dialysate, residual and total C, and Kt/V urea, daily dialysate albumin and β₂-microglobulin excretion, and clearance and daily dialysate glucose resorption were calculated over the 18-mo observation period.

The body mass index (BMI, kg/m²), an index of relative obesity, is calculated as the ratio of weight and height². Height and BMI were expressed as SD scores (SDS) according to the formula (xi − x̄)/SDm, where xi is the value of an individual, and x̄ and SDm are the gender- and age-specific mean and SD values of the normal population. The height standards of the Zurich Longitudinal Growth Study (17) and the BMI standards published for French children (18) were used as reference values. BMI SDS were calculated based on height age rather than chronological age to account for the patients’ growth retardation.

Relative height velocity was calculated by the change in height SDS during the observation period. To make use of all available height measurements and to reduce the distorting effects of singular measurement errors, a linear regression line was calculated for each individual patient from all height SDS values obtained within the observation period, and the slope of the regression line was used to express the annual change in height SDS. Only height data obtained within the first 18 mo were included in each individual’s regression analysis, even if additional follow-up observations had been made. The same procedure was carried out to calculate the annual change in BMI SDS.

The PET results were analyzed: (1) by considering the dialysate to plasma (D/P) creatinine and D/D₀ glucose equilibration ratios at 4-h dwell time; and (2) by calculating the creatinine and glucose equilibration rates defined by linear regression of all log-transformed D/P or D/D₀ ratios versus time (12). Making use of all measurements obtained during a test, the latter parameter is believed to yield a more stable reflection of the patient-specific peritoneal transport pattern.
For categorical comparisons, low/low-average and high/high-average transporters were separated by a cutoff 4-h D/P creatinine ratio of 0.71 (i.e., median of all patients studied) in the initial PET. The high-transporter state was defined by a 4-h D/P creatinine ratio of >0.89, comprising the upper 20% of individual creatinine equilibration curves in the group of patients studied. These cutoff values are close to the mean and +1 SD values obtained using 1000 ml/m² fill volume in the total population of the Mid-European Pediatric Peritoneal Dialysis Study (213 patients) (19).

**Statistical Analyses**

After testing the mode of distribution by the Shapiro-Wilks statistic, between-group differences of normally distributed variables were evaluated by t tests, and variables with skewed distribution by Wilcoxon sign-rank tests. Pearson correlation coefficients were calculated to assess possible associations between the measures of solute clearance and the indicators of growth and nutrition. The impact of categorical variables (rhGH treatment, transporter state) on the relative risk for growth failure was assessed by Mantel-Haenszel statistics. To evaluate which of the factors identified as significant in the univariate analysis were independent predictors of the course of growth and nutrition, stepwise multiple linear regression analyses were performed. The backward elimination mode with an elimination cutoff level of $P = 0.10$ was used.

**Results**

**Baseline Evaluation**

The most important anthropometric, biochemical, and dialysis-related characteristics of the study population at study entry are given in Table 1. Initial body height was below the third percentile in 31 patients (61%). The degree of growth retardation was independent of age or duration of dialysis. BMI was below the third percentile for height age in eight patients (16%). BMI SDS at study entry was positively correlated with age ($r = 0.36$, $P = 0.01$) and even better with direct parameters of body size, e.g., weight ($r = 0.49$, $P < 0.0005$). Also, a significant positive correlation existed between BMI SDS and the duration of prior dialysis at study entry ($r = 0.32$, $P < 0.05$).

The daily creatinine excretion rate normalized to body surface area was strongly correlated with age ($r = 0.51$, $P < 0.0005$) and all indices of body size (e.g., body surface area: $r = 0.55$, $P < 0.0001$). Creatinine excretion was also correlated with PNA ($r = 0.47$, $P < 0.001$), but not with dialysate protein losses ($r = -0.18$, $P = 0.22$).

APD patients had significantly more daily dialysis cycles (6.4 ± 2 versus 4.1 ± 1, $P < 0.0001$) but lower exchange volumes than patients on CAPD (824 ± 185 versus 1019 ± 174 ml/m², $P = 0.001$). Total daily dialysis fluid turnover was 5.29 ± 1.93/m² in APD compared with 4.22 ± 1.43 L/m² in CAPD patients ($P < 0.05$). Although the weekly dialysate $C_{Cr}$ was similar in CAPD (36 ± 13.73 m² per wk) and APD patients (38 ± 20), higher weekly dialysate $Kt/V$ urea values were achieved in APD (2.23 ± 0.83) than in CAPD patients (1.68 ± 0.55, $P < 0.01$). Total weekly $C_{Cr}$ also was not different in CAPD and APD patients (47 ± 15 versus 58 ± 29 L/1.73 m² per wk), whereas total $Kt/V$ was higher in APD (2.75 ± 0.97) than in CAPD patients (1.91 ± 0.57, $P < 0.01$).

The initial PET results showed a mean 4-h creatinine D/P ratio of 0.71 ± 0.20 (range, 0.19 to 1.0) and a mean D/D₀ creatinine glucose ratio of 0.36 ± 0.12 (0.11 to 0.57). D/P creatinine and D/D₀ glucose at 4 h were independent of age, body size, or standardized height or body mass (height SDS, BMI SDS).

**Table 1.** Initial anthropometric, biochemical, and PD characteristics in 51 children with end-stage renal failure followed for 18 mo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD (range)</th>
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<tbody>
<tr>
<td>Height SDS</td>
<td>-2.02 ± 1.59 (-6.6 to +0.1)</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-0.15 ± 1.7 (-2.91 to +5.57)</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>40.1 ± 5.8 (23.3 to 49.4)</td>
</tr>
<tr>
<td>Serum creatinine (g/dl)</td>
<td>5.8 ± 2.4 (1.5 to 10.6)</td>
</tr>
<tr>
<td>Blood urea nitrogen (g/dl)</td>
<td>57 ± 20 (23 to 100)</td>
</tr>
<tr>
<td>Residual GFR (in nonanuric patients) (L/1.73 m² per wk)</td>
<td>29 ± 24 (1 to 104)</td>
</tr>
<tr>
<td>PNA (g/kg per d)</td>
<td>1.08 ± 0.61 (0.40 to 3.37)</td>
</tr>
<tr>
<td>Creatinine excretion rate (g/1.73 m² per d)</td>
<td>0.51 ± 0.30 (0.16 to 1.34)</td>
</tr>
<tr>
<td>Exchange volume (ml/m²)</td>
<td>910 ± 200 (250 to 1460)</td>
</tr>
<tr>
<td>Dialysis fluid turnover (L/m² per d)</td>
<td>4.82 ± 1.79 (1.49 to 9.41)</td>
</tr>
<tr>
<td>Dialysate glucose concentration (g/L)</td>
<td>19 ± 5 (13.6 to 33)</td>
</tr>
<tr>
<td>Dialysate $C_{Cr}$ (L/1.73 m² per wk)</td>
<td>37 ± 17 (17 to 109)</td>
</tr>
<tr>
<td>Total $C_{Cr}$ (L/1.73 m² per wk)</td>
<td>53 ± 24 (17 to 136)</td>
</tr>
<tr>
<td>Dialysate $Kt/V$ urea</td>
<td>1.96 ± 0.77 (0.49 to 4.41)</td>
</tr>
<tr>
<td>Total $Kt/V$ urea</td>
<td>2.3 ± 0.89 (1.0 to 4.41)</td>
</tr>
<tr>
<td>PET 4-h D/P creatinine</td>
<td>0.71 ± 0.20 (0.19 to 1.02)</td>
</tr>
<tr>
<td>PET 4-h D/D₀ glucose</td>
<td>0.36 ± 0.12 (0.11 to 0.57)</td>
</tr>
</tbody>
</table>

*a* SDS, SD score; BMI, body mass index; PNA, protein equivalent of nitrogen appearance; $C_{Cr}$, creatinine clearance; PET, peritoneal equilibration test; D/P, dialysate to plasma concentration ratio; D/D₀, dialysate to dialysate at time 0 concentration ratio.
However, 4-h D/D₀ glucose was weakly negatively correlated with the cumulative duration of dialysis at time of the initial PET ($r = -0.32, P < 0.05$).

While residual GFR was positively correlated with age ($r = 0.37, P < 0.01$), similar dialysate and total creatinine and urea clearances were achieved in children of all age groups.

Twelve patients had been excluded from analysis due to PD technique failure and the necessity to switch to hemodialysis during the 18-mo observation period. Of note, in the initial PET these patients had low 4-h D/D₀ glucose (0.24 ± 0.07) and high D/P creatinine ratios (0.76 ± 0.20). In contrast, they did not differ from the total sample with respect to their mean (dialytic or total) creatinine clearance or Kt/V urea values.

**Longitudinal Development of Anthropometric, Clearance, and Peritoneal Transport Characteristics**

During the 18-mo study period, the degree of growth retardation did not change significantly (mean height SDS −2.11 ± 1.27). BMI SDS slightly increased by a mean of 0.28 ± 0.73 SD units per year (significantly different from 0, $P < 0.05$), resulting in a mean BMI SDS of +0.03 ± 1.66 during the observation period. Serum albumin remained stable at a mean concentration of 40.5 ± 8.3 g/L. The creatinine excretion rate slightly increased by 0.04 ± 0.25 g/1.73 m² per yr, reflecting the physiologic increase of fractional lean body mass during childhood.

Total small solute clearances remained stable throughout the study period, with a mean total C₅₀ of 55 ± 21 L/1.73 m² per wk and a mean total Kt/V urea of 2.42 ± 0.7. The stable total clearance pattern resulted from a significant decrease in residual GFR (−3.5 ± 10.6 L/1.73 m² per wk per year, change significantly different from 0, $P < 0.001$) compensated by an increase in dialytic C₅₀ (+9.6 ± 19.4 L/1.73 m² per wk per year, $P < 0.0005$) and Kt/V urea (+0.21 ± 0.63 per year, $P < 0.05$). The increase in dialytic solute removal was achieved by an expansion of total fluid turnover (+570 ± 1260 ml/m² per d per year, $P < 0.01$) to a mean of 5.36 ± 1.40 L/m² per d. In addition, a slight rise of the individual peritoneal transport rates was observed (e.g., the 4-h D/P creatinine ratio increased at an annual rate of +0.04 ± 0.12, $P < 0.05$). Of note, mean dialytic C₅₀ was positively correlated ($r = 0.35, P < 0.01$) and the D/D₀ glucose ratio was negatively correlated with the total duration of dialysis ($r = -0.31, P < 0.05$).

**Univariate Analysis of Factors Affecting Outcome Parameters**

The longitudinal change in height SDS was negatively correlated with the creatinine equilibration rate ($r = -0.33, P < 0.05$) and the 4-h D/P creatinine ratio in the initial PET ($r = -0.29, P < 0.05$). Patients who were classified as low or average transporters as defined by a 4-h D/P creatinine ratio of <0.89 displayed percentile-parallel growth within the subsequent 18 mo (mean change in height SDS: −0.10 ± 0.59 per year, not significantly different from 0), whereas high transporters diverged from the percentiles (change in height SDS: −0.50 ± 0.27, difference significantly different from 0, $P < 0.005$) (Δ height SDS difference high versus average/low transporters: $P < 0.005$). The high transporter state was associated with a relative risk of 6.55 (95% confidence interval 1.31 to 32.6, $P < 0.05$) to develop a negative slope of the height SDS regression line. The high transporters did not differ from the other patients with respect to age (median 7.6, interquartile range [iqr] 2 to 12 yr versus 8.7, iqr 6 to 11 yr; NS) or duration of dialysis (5.4, iqr 2 to 30 mo versus 4.4, iqr 1 to 10 mo; NS). Also, rhGH was administered in a similar proportion of high transporters (3 of 11) and low/average transporters (16 of 40, difference NS). The annual change in height SDS was slightly but not significantly higher in the 19 patients who received rhGH during the observation period (+0.03 ± 0.4) than in patients who remained untreated (−0.16 ± 0.6). The association between the change in height SDS and the D/P creatinine observed in the initial PET was similar in rhGH-treated ($r = -0.34$) and untreated patients ($r = -0.33$).

Neither the time-averaged dialytic nor the total creatinine or urea clearance was correlated with growth rates during the observation period. The mean residual GFR was positively correlated with mean height SDS ($r = 0.34, P = 0.01$), but not with the change in height SDS, suggesting that this association reflected the less marked growth retardation in patients with less severe disease. Subgrouping of the patients showed a similar mean annual change in height SDS in patients with (−0.08 ± 0.43) and without (−0.13 ± 0.79) residual renal function. Also, the trend toward a negative association between the change in height SDS and D/P creatinine was similar in nonanuric ($r = -0.27$) and anuric ($r = -0.44$) patients. The mean dialytic β₂-microglobulin excretion rate tended to be correlated with the change in height SDS ($r = -0.27, P = 0.06$).

The change in BMI SDS was negatively correlated with age ($r = -0.45, P < 0.001$). Children under age 4 yr increased by a mean of 0.92 ± 0.94 SD units per year (change significantly different from 0, $P < 0.01$), whereas children 4 yr or older showed stable BMI SDS patterns (change 0.1 ± 0.55 SD units per year). The pattern of body mass acquisition differed significantly between the two age groups ($P < 0.001$). Whereas dialysate or total small solute clearances showed no relationship with the longitudinal change in BMI SDS, the slope of the BMI SDS regression line was positively correlated with the rate of creatinine equilibration in the initial PET ($r = 0.35, P < 0.05$). Patients with a high-average or high transporter state had a slightly increased relative risk to gain relative body mass (1.85; 95% confidence interval, 0.93 to 3.66; $P = 0.09$).

The relative duration of rhGH treatment correlated positively with mean BMI SDS during the study period ($r = -0.30, P < 0.05$). Serum albumin appeared to be mainly determined by peritoneal losses. Both the time-averaged mean albumin concentrations and the relative change in serum albumin during the observation period were negatively correlated with mean daily albumin loss (measured in 26 patients) ($r = -0.49, P < 0.01$ and $r = -0.37, P = 0.05$, respectively). Similarly, the total daily dialisate turnover was negatively associated with the mean and change in serum albumin concentrations, respectively ($r = -0.36, P = 0.01$ and $r = 0.33, P < 0.05$). Mean C₅₀ was not predictive of serum albumin levels, and the mean
total total Kt/V was even weakly negatively correlated with mean serum albumin ($r = -0.31, P < 0.05$).

PNA was positively correlated with total Kt/V ($r = 0.52, P < 0.0001$), total $C_{Cr}$ ($r = 0.46, P < 0.0001$), and residual GFR ($r = 0.43, P < 0.0001$). Of note, the cumulative duration of rhGH treatment showed a weak positive association with PNA ($r = -0.28, P = 0.05$).

**Multivariate Analysis of Factors Affecting Outcome Parameters**

In the stepwise linear regression analysis, the following variables were assessed for simultaneous significant effects on the main outcome parameters ($\Delta$ height SDS, $\Delta$ BMI SDS, $\Delta$ serum albumin): the PET transporter state (1 = high versus 0 = average/low), dialytic $C_{Cr}$ or Kt/V urea, residual GFR, dialysate protein loss, age, and rhGH treatment (1 = yes, 0 = no). Three variables qualified as simultaneous significant predictors of the change in height SDS: the transporter state (negative effect, partial $r^2 = 0.07$), dialytic creatinine clearance (positive effect, partial $r^2 = 0.11$), and total dialysate volume (negative effect, partial $r^2 = 0.04$). The only variable included in the multiple regression analysis of the change in BMI SDS was patient age ($r^2 = 0.11$). When age was omitted from the list of potential predictors, total dialysate turnover qualified as a positive (partial $r^2 = 0.11$) and rhGH treatment as a weak negative predictor of the relative change in BMI (partial $r^2 = 0.05$). Finally, the change in serum albumin was affected positively by the mean total dialysate volume (partial $r^2 = 0.14$) and negatively by the mean protein loss (partial $r^2 = 0.06$).

**Discussion**

This study represents the first prospective evaluation of the role of the peritoneal transporter state and dialysis efficacy on patient outcome in children on chronic PD. Because patient mortality is exceedingly low and more sophisticated parameters of patient morbidity are difficult to study in children, growth, the change in relative body mass, and serum albumin were used as global indicators of patient well-being. In a longitudinal analysis of 51 children, we were able to demonstrate that both the transport properties and the intensity of dialysis independently affect the physical development of children on PD.

Within the past decade, the routine use of standardized PET has provided evidence that large interindividual differences in transperitoneal solute transport rates exist, even though peritoneal membrane properties are relatively invariable within an individual, allowing the classification of a patient’s individual transport status (20). Specific pediatric PET reference data have been provided (19,21). Adult patients with rapid small solute equilibration rates are at an excessive risk for adverse clinical outcomes and death (7,22–28). While increased peritoneal protein loss and subsequent malnutrition was originally assumed as the mechanism underlying increased morbidity of high transporters (23,24,29), recent evidence suggests that the high transporter state compromises clinical outcome regardless of serum albumin in adults (30). Increased cardiovascular morbidity due to poor ultrafiltration and chronic fluid overload has been postulated as an additional, nutrition-independent pathomechanism affecting patient outcomes in high transporters (31).

In this study, we demonstrate for the first time that the high transporter state is also an adverse risk factor for longitudinal growth in children on PD. The risk to develop growth failure (i.e., to lose height SDS) was increased severalfold in high transporters, who exhibited an average loss of 0.5 SD units per year of dialysis. This effect was independent of age and duration of dialysis. An even stronger association between the high transporter state and growth failure might have been missed because several high transporters were lost to follow-up because they had to be switched to hemodialysis treatment within the 18-mo observation period.

A point of concern was the possible confounding effect of rhGH treatment, which was administered to 37% of the patients. Although the open design of the study did not permit us to rule out such effects a priori, both univariate subgroup analysis and stepwise multivariate analysis suggest that the association between transporter state and growth was independent of rhGH treatment.

The pathophysiology of growth failure in uremic patients is complex and includes nutritional, endocrine, and metabolic aspects (32). Growth rates are correlated with residual GFR and are usually poorest in dialyzed patients, who show partial resistance even to pharmacologic growth stimulation by rhGH (33). This resistance has been explained by insufficient removal of accumulated uremic “toxins.” Our results suggest that at least for a subset of patients on PD, the possibility of exaggerated losses of substances relevant for growth must also be considered. These may include amino acids and proteins, vitamins and trace elements, or endocrine transmitters in the small polypeptide weight range. The weak negative association of dialytic $\beta_2$-microglobulin removal with growth rates is of note in this context. Alternatively, osmotic imbalances of the cellular milieu interieur as well as the growth plate matrix may interfere with cellular proliferation in high transporters, who are prone to insufficient ultrafiltration and fluid overload. Moreover, a relative insufficiency of insulin secretion in response to exaggerated continuous peritoneal glucose uptake might contribute to a more marked insulin resistance in these patients; the degree of insulin resistance has been shown to be inversely related to growth rates in dialyzed patients (34). Finally, it cannot be excluded that a common underlying mechanism predisposes for both the high transporter state and poor growth. Theoretically, genetic factors determining connective tissue ultrastructure and/or the regulation of capillary perfusion might affect both the cumulative growth potential and the peritoneal permeability of an individual.

The second issue addressed in this study concerned a possible association between small solute clearances and growth. Evidence for a positive relationship between small solute clearance and survival (1.5–7), clinical well-being (2.4), and neurophysiologic functions (3) was provided in adult PD patients, and standards of adequacy for small solute clearances have recently been defined (8).
Whereas previous studies in adult CAPD patients struggled with the small degree of clearance variability due to relatively uniform dialysis dose prescriptions, the power of this study was strengthened by the preferential use of APD resulting in a large variation of clearance. While we were not able to demonstrate a major impact of the dialysis dose or total small solute clearance on growth in the univariate data analysis, a positive effect of the mean total creatinine clearance on growth rates became apparent when controlling for the PET transporter state in the multivariate regression analysis. This may be explained by the high transporters’ tendency to achieve greater small solute clearances. On the population level, the adverse effect of the high transporter state might mask a weak intrinsically positive effect of higher clearances on body growth.

Changes in the patients’ nutritional state were assessed by the evolution of normalized BMI and serum albumin over time. A marked increase in BMI SDS with time on dialysis was observed in the infant population, whereas no net changes occurred in older children. Consequently, age was the most important determinant of the change in BMI SDS both in the univariate and in the multivariate analysis. Of note, the accelerated acquisition of body mass was not accompanied by better growth rates in the infants. The trend toward obesity in the young children is most likely explained by the consequent use of tube feeding in most infants, resulting in an adequate and sometimes excessive calorie intake. Another factor possibly contributing to enhanced body mass gain is dialysate glucose resorption, which is usually higher in young infants due to their enhanced permeability of the peritoneal membrane for small molecules (21). The role of peritoneal glucose resorption in the trend toward obesity is supported by the observed positive association of the change in BMI SDS with the PET transporter state in the univariate, and with total dialysis fluid turnover in the multivariate regression analysis.

Besides BMI SDS, the longitudinal change in serum albumin was evaluated as a possible indicator of the patients’ nutritional state. Mean serum albumin levels were in the normal range, and no net change occurred over time. Individual changes in serum albumin during the observation period were determined mainly by the daily albumin losses via the peritoneum, confirming results in adult patients (29). Total dialysate volume, a determinant of dialysate protein loss, was also a negative predictor of serum albumin in the univariate analysis, but became a positive codeterminant when albumin loss was accounted for in the multiple regression analysis. This may be interpreted by better fluid control in patients with a large dialysate turnover, resulting in less “diluted” serum albumin levels. The initial hypothesis that small solute clearance may be positively correlated with serum albumin as a marker of nutritional state was not confirmed; conversely, even a weak negative association was noted between Kt/V urea and serum albumin. In light of the observed dependence of serum albumin on protein loss and dialysate turnover, the latter finding may be explained by more marked albumin losses in high transporters who require more frequent APD cycles with large cumulative fluid turnover rates, but tend to achieve higher clearances. The dependence of serum albumin on fluid state and dialytic protein loss questions its usefulness as an indicator of nutrition. On the other hand, a strong and consistent predictive value of serum albumin for patient morbidity and survival was documented in adults (1,7,23,25,35,36); excessive cardiovascular risks in patients with low serum albumin secondary to poor fluid control were suggested to underlie this association independent of malnutrition. Although such fatal complications rarely occur in children, fluid overload is the most frequent cause of life-threatening events also in the pediatric PD population (37). Thus, while serum albumin appears to be a poor marker of nutrition in children on PD, its monitoring appears to be worthwhile in terms of fluid control.

In conclusion, our study provides evidence that the peritoneal transporter state is an independent determinant of growth and body mass acquisition in children on chronic PD. High transporters are at increased risk to grow poorly and become obese. The role of PD clearances for physical development is less evident. Although multivariate analysis suggests a positive effect of high PD doses on growth independent of the transporter state, the anthropometric results obtained in this study do not provide a clear rationale for adopting lower acceptable small solute clearance limits in children. Additional prospective studies, using more sophisticated parameters of clinical outcome, will be required to define PD adequacy in children.

Appendix

Participants of the Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS): M. Zimmering, T. Lennert (Berlin, Germany), U. Querfeld (Cologne, Germany), H. Ruder, M. Böswald (Erlangen, Germany), K.E. Bonzel (Essen, Germany), D.E. Müller-Wiefel (coordinator, Hamburg, Germany), G. Offner (Hannover, Germany), F. Schaefer, O. Mehls (coordinators, Heidelberg, Germany), J. Misselwitz (Jena, Germany), C. Greiner (Leipzig, Germany), G. Klaus (coordinator, Marburg, Germany), B. Klare (Munich, Germany), E. Simkova (Prague, Czech Republic), H.-J. Stolpe (Rostock, Germany), M. Fischbach (Strasbourg, France), E. Balzar (Vienna, Austria).

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