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Kt/V and nPNA in pediatric peritoneal dialysis: a clinical or a mathematical association?

Abstract The relationship between dialysis dose and nutrition is a field of particular interest in chronic pediatric dialysis (PD), and a positive correlation between ureaKt/V and nPNA has been published, suggesting a better nutritional status is associated with higher dialysis doses. However, this relationship has also been criticized as being the result of a mathematical coupling resulting from the same variables. The objective of the study was to establish the relationship between dialysis dose (Kt/V) and nutritional variables: daily protein intake (DPI), protein catabolic rate (PCR), protein equivalent of total nitrogen appearance (PNA) and nitrogen balance (NB) in dialyzed children. A cohort, prospective, observational study was carried out, for which 223 biochemical measurements were performed in 20 patients, ages 1 month to 14.3 years old (13 males), under PD for a 12-month period of follow-up. Monthly residual and total ureaKt/V, DPI, PCR, nPNA and NB were calculated, and the correlation between Kt/V and the nutritional parameters was evaluated. The Borah equation was used to calculate the nPNA. The data are reported as the mean plus or minus the standard error. All statistical comparisons were done with a paired *t* test, and two-way ANOVA for repeated measures was used to calculate correlations. A $P<0.05$ was considered significant. Mean total and residual Kt/V was 3.4±1.3 and 1.69±1.27, respectively; nPNA and PCR were 1.38±0.44 and 1.39±0.43 g/kg/day, daily protein intake (DPI) was 3.25±1.27 g/kg/day, and NB showed a value of 1.86±1.25 g/kg/day. A significant positive correlation was found between Kt/V and DPI, PCR, DPC and nPNA (all values $P<0.0001$), but no correlation was found between total and residual Kt/V vs. nitrogen balance (*P*:ns). Total Kt/V showed a significant positive correlation with nPNA, but it did not show any correlation with nitrogen balance, suggesting that the relationship with nPNA is the result of a mathematical association calculated from the same variables.

Keywords Dialysis dose · KtV · Protein equivalent of urea nitrogen appearance · PNA · Protein catabolic rate · Nitrogen balance · Peritoneal dialysis

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Introduction

Since the National Cooperative Dialysis Study (NCDS) in the 1960s, the attempt has been made to focus dialysis therapy through a quantitative approach [1]. The first parameter studied as a prognostic variable was the delivered dialysis dose or Kt/V. This parameter indicates the patient's solute clearance during a 7-day period, normalized to the body's volume of urea distribution, with both clearance and the volume of distribution expressed in liters; hence, the units for Kt/V in peritoneal dialysis (PD) are dimensionless, but this value is a useful parameter to calculate the amount of dialysis given to the patient [2, 3, 4, 5].

$$\mathrm{Kt/Vurea} = [24 - \mathrm{hdialysate(urine)volume(L)} \times \mathrm{D(U)/Purea} \times 7]/[0.60 \times \mathrm{weight\ (kg)}], \quad (1)$$

where D = dialysate urea nitrogen and U = urinary urea nitrogen [7].

The relationship between dialysis dose and morbidity/mortality has been shown by several studies. The CANUSA Study [6] in adults reported a 5% decrease in patient survival in association with every 0.1 decrease in total weekly Kt/V urea for Kt/V values between 1.5 and 2.3. A weekly Kt/V urea equal or greater than two per

week is the dialysis outcome quality initiative (DOQI) recommendation [7]. This value approximates a renal urea clearance of 7 ml/min and a renal creatinine clearance between 9 to 14 ml/min/1.73 m^2. In pediatric peritoneal dialysis, the DOQI Work Group suggests that the target dialysis dose should always meet or exceed the adult recommendations, and it should be maintained along with a protein intake greater than the recommended dietary allowances (RDA) [7, 8, 9]. The Ademex Study [10] was unable to find that the increased dose of peritoneal dialysis over a 2-year follow-up resulted in any reduction of mortality, but the importance of adequate nutrition was confirmed as a prognostic factor.

The second variable associated with a better outcome in peritoneal dialysis is nutritional status. Malnutrition has long been known to be a major determinant of morbidity as well as mortality in the adult dialyzed population, and eradicating it remains one of the most important goals in the management of children under chronic peritoneal dialysis therapy [2, 3, 9, 10, 11, 12, 13, 14]. Growth, morbidity and mortality in pediatric PD patients are closely related to nutritional status [11, 12, 13, 14], which need to be expressed through a number of laboratory parameters, such as nitrogen balance (NB), protein catabolic rate (PCR), daily protein intake (DPI) and the protein equivalent of urea nitrogen appearance (PNA) [13, 15, 16, 17].

For pediatric patients on PD, protein catabolic rate and nitrogen balance studies have been used to evaluate nutritional status, but recently, PNA has been suggested by DOQI guidelines to be the best tool with which to evaluate this condition [7, 12]. The final product of protein catabolism is urea, and nitrogen intake is almost entirely from protein; therefore, in steady state conditions, protein intake can be estimated from urea kinetics studies. Most of these studies in clinical practice are performed measuring the daily excretion of nitrogen in the urine, dialysate and feces, and then multiplying the total nitrogen excretion by 6.25, because 6.25 g of protein results in 1 g of nitrogen. However, the true protein catabolic rate is about six times higher than the PCR estimated from this urea appearance rate, as most of the catabolized protein is not catabolized to urea, but used for protein synthesis again. Therefore, PNA has been suggested to be a more accurate term than PCR for protein balance studies [6, 7]. The modified Borah equation has been recommended by DOQI for PNA evaluation in children, normalizing to g/kg/day, or nPNA [7, 18]. Although the growing evidence for the critical meaning of dialysis adequacy and nutrition in the long-term prognosis of dialyzed children is well-documented, peritoneal dialysis prescriptions are still largely empirical. Growth instead of mortality is the main prognostic variable in pediatric PD, and all nutritional recommendations should take into account that pediatric patients need a positive protein balance.

Based on the available evidence, it has become clear that a patient on peritoneal dialysis should be evaluated on a regular basis by Kt/V and PNA. Both parameters are linked to patient survival, and a positive correlation among them has been repeatedly reported in PD patients [19, 20], suggesting an increased appetite and a high protein intake as the dialysis dose increases. However, some studies have shown that Kt/V and PNA should be considered as cross-related rather than independent variables [2, 7, 8, 9, 11, 14], reflecting the fact that both parameters are mathematically interrelated [7, 19]. This is a very important point for clinical purposes, because nephrologists should be aware that when they are leading with one of these variables to adjust dialysis therapy, it will result in a change in the other simply because of the mathematical relationship.

The objective of this study was to establish the relationship among the dialysis dose (Kt/V) and nutritional variables [daily protein intake (DPI), protein catabolic rate (PCR), protein equivalent of total nitrogen appearance (PNA) and nitrogen balance (NB)] in pediatric patients under chronic peritoneal dialysis and to asses whether the relationship between ureaKt/V and PNA is a cause-effect or a simply mathematical association.

Patients and methods

A cohort, prospective, observational study was carried out in 20 stable PD patients, ages 1 month to 14.3 years old (13 males), for a 12-month period of follow-up. The mean time on PD at the time of enrollment in the study was 10 months (range: 1–23 months). The underlying renal disorders included renal dysplasia (n=9), reflux nephropathy (n=3), hemolytic uremic syndrome (n=1), obstructive uropathy (n=4) and chronic glomerulonephritis (n=3). At study entry, 7 patients were on CAPD, and 13 were on automated PD. Of the 20 patients, 2 had no residual renal function. No patient was studied within 1 month following a peritonitis episode. Patients with fever, infections, nephrotic syndrome, gastrointestinal absorption disturbances, steroid treatments, endocrine diseases, genetic syndromes and compliance or behavioral disturbances were excluded. At study entry, and every month for 12 months of follow-up, a 24-h dialysate and urine collection along with blood samples were collected on an outpatient basis. Timerosal was added to urine and dialysate samples in order to avoid the generation of urea secondary to bacterial activity. At the hospital, samples were evaluated for color and volume before being sent to the laboratory, and the parents were asked for any inconvenience during the collection period. All the samples obtained under non-compliance conditions were discarded. Creatinine (Jaffe reaction), urea nitrogen (enzyme assay), total protein and albumin (turbidimetric assay) were measured in plasma, urine and dialysate.

A weekly nutritional follow-up by telephone was performed during the 1st month of the study to monitor that there was an adequate protein and energy intake that met the DOQI recommendations [7]. Parents were instructed to control the usual food portions with an automatic food-weight device that was given to each patient at the beginning of the study. Once a month, a 24-h recall and food frequency questionnaire was used to estimate the intake of energy, macronutrients and micronutrients in order to correct any deviation from the protocol. Every time there was any doubt about the parent's management of food ingestion, the renal dietician performed a weekly phone evaluation for 2 weeks. The dialysis dose was expressed as residual and total ureaKt/V (see equation 1) in l/week. Nutrition was evaluated throughout the calculation of PCR.

$$\mathrm{PCR(g/kg/day)} = [(\mathrm{UUN} + \mathrm{DUN}) \times 6.25]/\mathrm{weight(kg)}, \qquad (2)$$

where UUN =24-h urinary urea nitrogen and DUN =24-h dialysate urea nitrogen [7], and of nPNA (the Borah equation):

$$\mathrm{PNA(g/d)} = (6,49 \times \mathrm{UNA}) + (0,294 \times \mathrm{V}) + \mathrm{proteinlosses\,(g/24h)}, \quad (3)$$

where UNA = urea nitrogen appearence (UUN + DUN) [7, 18], and total daily protein catabolism (DPC) and nitrogen balance (NB):

$$\mathrm{DPC} = (\mathrm{DUN24h} * 6.25) + (\mathrm{UUN24h} * 6.25 * 1.25) + (\mathrm{Albumin_d\ 24h}) + (\mathrm{Albumin_u\ 24h}) + (\mathrm{weight\ kg} * 0.045 * 6.25)(29) \quad (4)$$

$$\mathrm{NB} = \mathrm{DPI} - \mathrm{DPC}(30) \quad (5)$$

Correlations between Kt/V and nutritional parameters were evaluated.

Statistical study

Data are reported as the mean ± standard error. All statistical comparisons were done with a paired *t* -test, and two-way ANOVA for repeated measures was used to calculate correlations. $P < 0.05$ was considered significant. For the best association level, with a significance of 5%, a power greater to 90% was obtained. This result is reliable since although 20 patients were included, when counting on a design of repeated measures, each patient expands the sample six times. Stata v7.0 was used for all calculations.

Results

A total of 223 biochemical measurements were performed for each variable during a 12-month period of follow-up. Twenty stable patients under chronic peritoneal dialysis aged 1 month to 14.3 years (13 males) were evaluated. Stable patients were defined when all the clinical and biochemical routine measurements were under normal limits considering the uremic condition.

Mean total and residual Kt/V was 3.4±1.3 and 1.69± 1.27, respectively; peritoneal Kt/V was 1.71±0.68, UUN was 58.8±44.6 and DUN was 79.1±54.7 mg/kg/day, respectively.

Daily protein intake (DPI) was 3.25±1.27 g/kg/day, and nPNA and PCR were 1.37±0.44 and 0.84±0.31 g/kg/day, respectively. Daily protein catabolism showed a value of 1.38±0.39, and nitrogen balance was 1.86± 1.25 g/kg/day.

PNA expressed in g/kg/day showed a strong correlation with PCR and DPI ($P<0.001$, $r=0.9$) and daily protein intake ($P<0.001$, $r=0.6$).

A significant positive correlation was found between total Kt/V vs. DPI, PCR, DPC and nPNA (all values $P<0.0001$) (Table 1), but no correlation was found between totalKt/V vs. nitrogen balance (Table 1) (*P*=ns). Residual Kt/V showed the same positive associations as total Kt/V with nutritional variables, but again, it did not show a significant correlation with nitrogen balance.

Table 1 Mean values for dialytic and nutritional variables in 20 PD patients followed by 12 months and 223 biochemical measurements. *PNA* protein equivalent of urea nitrogen appearance in g/kg/day. Daily protein intake and protein catabolic rate are expressed in g/kg/day

	Mean	SD	*P*
Total KtV	3.4	1.3	*
Residual KtV	1.69	1.27	*
Daily protein intake	3.25	1.27	*
Protein catabolic rate	0.84	0.31	*
PNA	1.37	0.44	*
Nitrogen balance	1.86	1.25	**

* $P<0.001$; ** *P*=nonsignificant. All calculations were made by two-way ANOVA for repeated measures

Discussion

The outcome for patients under chronic peritoneal dialysis has been often linked to dialysis dose and nutritional status, and positive correlations between nPNA and clearance of urea or creatinine have been reported repeatedly in PD subjects [2, 3, 4, 7, 8, 9, 15, 16, 19]. This is an area of particular interest, with a correlation between ureaKt/V and PCR suggested by previous studies [7, 19, 20], assuming that PCR was dependent upon the type and amount of treatment in dialyzed uremic patients. In that sense, the possibility of an improved patient outcome with increased dialytic dose has been suspected to be a consequence of a better nutritional status (measured as PNA) in response to the higher Kt/V applied. However, this relationship has been criticized as being the result of mathematical coupling without a clinical significance [7, 19]. In other experiences, nPNA tends to increase after Kt/Vurea has been increased, and Aranda et al. [21] found that seven children with a mean Kt/Vurea of 3.0±0.4 had a significantly higher nPNA compared to other children with a lower total Kt/Vurea. Schaefer et al. [22] found that PNA was positively correlated with total Kt/V, but neither the time-averaged dialytic nor the total creatinine or urea clearance was correlated with growth rates during the observation period. On the other hand, adult studies have shown no correlation with PNA after increasing the dialysis dose. Davis et al. [23] analyzed the net effect of increasing the dialysis dose to malnourished adult dialyzed patients, increasing the peritoneal Kt/Vurea 22.5%, without reaching any increase in protein intake, as judged by dietetic interview or protein nitrogen appearance. Van Hoeck et al. [24] examined the nutritional effects of increasing the dialysis dose in eight children on peritoneal dialysis, without confirming any impact on daily protein or caloric intake.

The mean nPNA of 1.37±0.44 in our patients is higher than the DOQI recommendations [7] and those reported in European Group communications [22], showing significant correlation with other nutritional variables, DPI and PCR ($P<0.001$), as well as with dialysis dose, both residual and total Kt/V ($P<0.0001$, $r=0.79$ and 0.75, respectively). In our experience, as well as that expressed in other communications [15, 22, 24, 26], children tend to

show a greater Kt/V and nPNA than the adult dialyzed population, an expected result because of the higher protein requirements in young patients secondary to growth along with a greater loss of albumin in dialysate [22, 25, 27]. Schaefer et al. [22] showed that serum albumin appeared to be mainly determined by peritoneal losses in dialyzed children, and 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 in that study.

The relationship between Kt/V and PNA, if real, should also be found with other nutritional indices, especially nitrogen balance, which represents the more accurate measure of nutrition in clinical practice [18, 28, 29, 30]. Nitrogen balance calculations are often used for research and clinical purposes, with the knowledge of nitrogen loss being central to this evaluation. Total nitrogen appearance (TNA) is the sum of all outputs of nitrogen from the body, dialysate, urine and feces, in the form of urea, protein, peptides, amino acids and all other nitrogen-containing products, and in steady-state patients, TNA plus any unmeasured nitrogen losses should roughly equal the total nitrogen intake. Because the final product of protein catabolism is urea, and nitrogen intake is almost entirely from protein, in steady state conditions protein intake can be estimated from TNA [29, 31]. UUN has often been used to approximate total urinary nitrogen (TUN), because the laboratory methods, like the Kjeldahl method, to measure TUN are time consuming and involve the use of corrosive materials. For that reason, several adjustment formulae have been applied to calculate TUN from the measured UUN, to compensate for nonurea and insensible nitrogen losses. The fourth equation detailed above was used in this study, multiplying UUN ×1.25, assuming that UUN composes approximately 80% of TUN, and then correcting by 6.25 to express TUN as protein. A second adjustment is required to compensate for insensible nitrogen losses, which can be obtained by multiplying the weight in kg by 0.045 [30, 31]. Stool nitrogen losses were approximated to circumvent the problem of extended stool collections, as pointed out in equation 4. This is a common practice in nitrogen balance studies, assuming approximately 40–60 mg/kg of daily fecal losses of nitrogen and 15 mg/kg of daily cutaneous losses [31, 32]. The resultant value should closely reflect daily protein catabolism, and when subtracted from DPI, will express the nitrogen balance for each patient [30, 34]. This calculation should be of great value for the pediatric population, because the protein equivalent of nitrogen appearance that occurs in children differs from that seen in adults, mainly because children are growing, and they are not in a nutritional steady state as occurs in adult populations. As expected, Kt/V showed a strong positive association with all the variables containing the same parameter, urea nitrogen, which include DPI, PCR, DPC and PNA. The significant relationship founded between Kt/V and PNA could not be reproduced when the ANOVA model for repeated measures was applied to nitrogen balance. The absence of this relationship between dialysis dose and the above-described nitrogen balance studies suggests that Kt/V and PNA are more mathematically related than representative of a real clinical cause-effect association as proposed elsewhere.

The experience gained from patients who had their urea Kt/V increased by changes in dialysate volume or by changes to CCPD showing a later improvement in PNA should be carefully interpreted before assuming that a better nutritional condition could be obtained after increasing the amount of dialysis. In those children, a dialysis dose higher than the recommended one could result in a nutritionally compromised status rather than the expected good nutritional outcome.

Other variables related to protein intake can also affect the outcome in pediatric PD patients. A persistent negative correlation has been found in PD patients between protein intake, nPNA and plasma bicarbonate in our experience and by other authors ($P<0.001$, $r=0.51$) [35, 36, 37]. There is increasing evidence that metabolic acidosis is an important stimulus for net protein catabolism and malnutrition, as well as that protein intake means an acid load for the metabolism. [37, 38, 39, 40]. The catabolic effect of acidosis seems to be mediated by the stimulation of the proteolytic activity in the skeletal muscle tissue secondary to an activation of the transcription of genes for proteolytic enzymes in muscle [41]. The stimulation of the skeletal muscle branched-chain aminoacid decarboxylation will increase the catabolism of branched-chain amino acids, like valine, leucine and isoleucine, which are mainly metabolized in muscle tissue [12]. A low intracelular valine concentration in muscle was found to be correlated with the pre-dialysis blood standard bicarbonate levels between 18–24 mmol/l in hemodialyzed patients, suggesting that slight and intermittent acidosis in uremic patients may stimulate the catabolism of valine in muscle, resulting in valine depletion that may be a limiting factor for protein sysnthesis (Heimburger). These observations correlate closely with our results when body composition was studied by DEXA in this group of patients [35]. DPI showed a negative correlation with bone mineral density and bone mineral content, as well as with plasma bicarbonate, suggesting that an excess of protein intake can be dangerous for the outcome for these patients and making clear that full correction of acidosis should be attempted when treating PD children [38].

We believe it is important that prospective studies in pediatric patients be carried out in which the ureaKt/V is manipulated by different dialysis techniques, while nPNA and other nutritional parameters like nitrogen balance are followed to confirm the exact relationship between them.

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