

Renal Osteodystrophy in Pediatric Patients on Peritoneal Dialysis

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Renal osteodystrophy (ROD) is one of the most frequent complications in pediatric uremic patients on peritoneal dialysis (PD), and each case requires a different therapeutic approach. In the present study, we characterized ROD in pediatric patients on chronic PD.

We studied 20 patients (12 boys, 8 girls) for a 12-month period. The mean age of the patients was 5.82 ± 5 years. We allocated each patient to one of three groups according to intact parathormone (iPTH) value: group 1, iPTH ≤ 150 pg/mL, n = 12; group 2, iPTH 151 – 400 pg/mL, n = 2; and group 3, iPTH ≥ 401 pg/mL, n = 6. Monthly, we recorded plasma calcium, phosphorus, and alkaline phosphatase; Kt/V; normalized protein equivalent of total nitrogen appearance (nPNA); and calcitriol dose. Growth was registered as the Z height/age. Student t-test and analysis of variance for repeated measures were used for the statistical analyses. A value of $p < 0.05$ was considered significant.

All 20 patients completed 6 months of follow-up; 9 patients completed 12 months. At months 1, 6, and 12, vitamin D doses for groups 1 and 3 were significantly different ($p < 0.05$), as expected. Mean values of iPTH for groups 1 and 3 were 52 ± 47 pg/mL and 1239 ± 718 pg/mL respectively, $p < 0.05$. At 6 months' follow-up, iPTH values had changed to 163 ± 177 pg/mL for group 1 and 544 ± 249 pg/mL for group 3 ($p < 0.05$), but for group 3 that trend was lost at 12 months' follow-up, when their mean iPTH value rose to 972 ± 420 pg/mL. Patients who had been started on PD less than 6 months before entering the study (60% of patients) showed a mean iPTH value of 629.13 pg/mL. Patients with more than 6 months on dialysis before entering the study showed an iPTH value of 115.53 pg/mL ($p < 0.05$).

At 6 months' follow-up, iPTH values in groups 1 and 3 both showed a change toward the value range

for group 2. At month 12, iPTH values in group 1 continued to show the same tendency, but iPTH values in group 3 showed a tendency to return to their initial levels. Low-turnover ROD was highly prevalent in the study, correlating strongly with time on dialysis.

Key words

Renal osteodystrophy, calcitriol, bone, parathormone

Introduction

Renal osteodystrophy (ROD) is a multifactorial disease that affects children with chronic renal failure (CRF). It leads to bone deformities, fractures, bone pain, and growth failure (1,2). A large body of accumulated evidence indicates that the derangements in mineral and bone metabolism in CRF patients are associated with increased morbidity and mortality. Evidence shows that, early in the course of renal insufficiency, phosphorus accumulation at the cellular level can suppress renal 1α -hydroxylation of vitamin D, reducing the circulating level of that hormone, which in turn leads to a reduction in the intestinal absorption of calcium and an impaired calcemic response to parathormone (PTH). Those two abnormalities contribute to a hypocalcemic state that leads to secondary hyperparathyroidism (2,3).

Available data also show that 1,25-dihydroxyvitamin D₃ may have a direct effect on the parathyroid gland. That hormone reduces prepro-PTH messenger RNA at the parathyroid cells and renders the parathyroid gland more susceptible to the inhibitory effect of ionized calcium. *In vivo* and *in vitro* tests have shown that 1,25-dihydroxyvitamin D₃ can directly suppress the activity of the parathyroid cells. A deficiency of the hormone could therefore result in secondary hyperparathyroidism even without overt hypocalcemia. In addition, it has been demonstrated that hyperphosphatemia *per se* may stimulate parathyroid hormone synthesis by a post-transcriptional effect on PTH gene expression (2–4).

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Hyperparathyroidism affects almost all patients with CRF. The integration of various pathogenic factors is currently accepted as the cause of this complication. Later in the course of CRF, other factors—malnutrition, acidosis, and therapeutic agents such as diuretics and steroids—can affect bone metabolism, leading to a more complicated biochemical and clinical picture (5,6). The role of aluminum toxicity in low-turnover bone disease has been long recognized, and aluminum is therefore no longer used as a phosphorus binder in the treatment of pediatric patients (7).

When treating children with CRF, it is important to remember that bone disease is usually asymptomatic at the beginning of renal insufficiency. Clinical symptoms and manifestations appear only late in the course of ROD. By the time symptoms occur, biochemical abnormalities, hypocalcemia, hyperphosphatemia, high levels of parathormone, and low levels of 1,25-dihydroxyvitamin D₃ are well established (8). At that time, histopathologic abnormalities in bone are clearly evident [histomorphometric analysis of undecalcified bone biopsy specimens being the only method for absolutely identifying the pathologic processes occurring in ROD (3)].

However, the type of bone disease can vary from one CRF patient to another. The pathologies (2,9,10) range from high-turnover disease—with its enhanced number and activity of osteoclasts, leading to increased bone resorption and to replacement of normal lamellar bone with coarse collagen fibers and irregular mineralization (“woven bone”)—to low-turnover disease—in which normal bone activity is reduced, leading to increased unmineralized osteoid content (as seen in osteomalacia) or to decreased trabecular bone (as seen in the adynamic form of the disease). Some patients may have a single type of bone disease; others can show mixed abnormalities. As a result, treatment of ROD is a continuing challenge for nephrologists.

The development, during the past decade, of highly precise radioimmunometric assays for intact PTH (iPTH) resulted in serum iPTH concentration being recommended as a useful predictor of bone histology type. And assays for iPTH are useful for repeated noninvasive evaluation of patients with CRF—at least when large groups of patients are studied (11). However, in individual cases, it is not always possible to use serum iPTH concentration as an exact predictor

of bone histomorphometry. Recent data suggest that serum iPTH concentrations 3.5 times above the upper limit of normal have a positive predictive value of 97% in the diagnosis of high-turnover bone disease. Other data have shown that serum iPTH values below 100 pg/mL are positively correlated with low-turnover bone histology (11–13). The guidelines from the Dialysis Outcomes Quality Initiative (DOQI) suggest that a serum iPTH level less than 100 pg/mL reliably predicts the presence of adynamic bone disease, and a serum iPTH level greater than 500 pg/mL is frequently associated with high-turnover disease (10).

The most extended kind of therapy for ROD patients is the active form of vitamin D, 1,25-dihydroxyvitamin D₃ (calcitriol). But in pediatric practice, definitive recommendations for vitamin D dosage, duration of treatment, and even the route to be used, have not been possible.

Osteitis fibrosa (high-turnover bone disease) has long been recognized as the most common form of ROD in children. But that picture has undoubtedly changed in recent years, because high doses of calcitriol have been administered by the oral, intraperitoneal, and intravenous route in an attempt to suppress the high levels of iPTH commonly found. On the other hand, the use of vitamin D sterols to treat secondary hyperparathyroidism can lead to the development of adynamic renal osteodystrophy, particularly in patients who also are given large oral doses of calcium to manage hyperphosphatemia. Adynamic bone lesions have been described when plasma iPTH levels were lowered too far during calcitriol therapy, reaching the low serum iPTH values usually associated with adynamic bone in patients who are not receiving vitamin D therapy (6,14–18).

At the beginning of therapy, we have observed high iPTH plasma values in uremic children on peritoneal dialysis (PD). All of them receive treatment with calcitriol. Some develop low serum iPTH (16); others seem to be resistant to vitamin D, and their iPTH levels remain higher than expected even if they receive the same initial dose of vitamin D as the responders. We needed to clarify how much and how long patients should be treated to achieve the best “ROD state” while awaiting a renal transplant.

Our objective in the present study was (A) to describe, from a biochemical point of view, the spectrum of ROD in children on PD; (B) to measure the response of our pediatric population to treatment with

calcitriol; and (C) to correlate changes in serum iPTH level with dialytic and nutritional variables.

Patients and methods

We conducted our prospective study in pediatric patients on ambulatory PD attending the Luis Calvo Mackenna Children's Hospital during the period January 2002 to June 2003. All patients received calcitriol therapy, erythropoietin, and iron. Patients were excluded from the study if they had any of these conditions: peritonitis during the 2 months preceding study entry, nephrotic syndrome, intestinal absorption diseases, chronic diarrhea, neurologic diseases that interfered with oral feeding, chronic or recurrent infections, chronic steroid use, endocrine disturbances, metabolic diseases, treatment with growth hormone, and HIV-positive or hepatitis B surface antigen-positive serology. All patients received nutritional support and a dialysis dose in keeping with the DOQI recommendations (10).

At months 1, 6, and 12 of follow-up, iPTH levels in plasma were measured according to the recommended method (10). At entry into the study, patients were assigned to one of three groups according to serum iPTH value: group 1, iPTH \leq 150 pg/mL; group 2, iPTH 151–400 pg/mL; and group 3, iPTH \geq 401 pg/mL. The iPTH values were chosen for their predictive value with regard to bone histology (11–14). Monthly, we evaluated nutritional parameters, calcemia, phosphatemia, alkaline phosphate, pH, bicarbonate, albuminemia, and dialytic variables.

We prescribed calcitriol in doses of 0.01–0.05 μ g/kg daily. Oral drops (One-Alpha: Leo Pharma, Malmö, Denmark) was used in patients who could not swallow capsules. In group 1 patients, calcitriol was used twice weekly at the start of therapy. In patients with a plasma iPTH less than 150 pg/mL after 3 months of treatment, calcitriol was discontinued for 30 days. In group II patients, the calcitriol was given every 48 hours. In group III patients, the dose was administered daily. If iPTH values did not change after 3 months in group 3 patients, the daily dose was doubled. If plasma iPTH remained above 1000 pg/mL, the patient was treated with pulses of oral calcitriol.

Statistical analysis

Data are reported as mean \pm standard error. All statistical comparisons used the paired *t*-test, and $p < 0.05$ was considered significant. Two-way analysis of vari-

ance for repeated measures was used to calculate correlations.

Results

We enrolled 20 children (12 boys, 8 girls) into the study. All 20 patients completed 6 months of follow-up; 9 patients completed 12 months. Groups 1, 2, and 3 accumulated 12, 2, and 6 patients respectively. Table I shows the distribution of the patients according to sex and iPTH value. Mean age of the patients was 5.82 ± 5 years (range: 0.17–14.83 years). Mean time on PD at entrance into the study was 11.2 ± 14.13 months (range: 0–46 months). Time on PD was longer for the group 1 patients as compared with those in group 3 ($p < 0.05$).

The mean iPTH value in patients who started PD less than 6 months before entering the study (60% of them) was 629.13 pg/mL. For patients who had been on PD for more than 6 months, mean iPTH was lower: 115.53 pg/mL, $p < 0.05$. Before entering the study, 35% of patients had been on PD for more than 1 year, and 15% had been on PD for more than 2 years. All patients who started dialysis at least 1 year before recruitment were included in group 1 (30% of the patients). Table II shows the analyzed variables by group.

At months 1, 6, and 12, the doses of vitamin D for groups 1 and 3 were significantly different ($p < 0.05$), as expected. In analyzing response to therapy, we observed that the serum iPTH values from month 1 in groups 1 and 3 (mean values: 52 ± 47 pg/mL and 1239 ± 718 pg/mL respectively, $p < 0.05$) had moved toward the "normal" range at 6 month' follow-up, reaching a mean value of 163 ± 177 pg/mL for group 1 and 544 ± 249 pg/mL for group 3 ($p < 0.05$). However, in group 3, that trend was lost at month 12 of follow-up, when mean iPTH values rose to 972 ± 420 pg/mL (range: 330–1470 pg/mL) in that group. The change in serum iPTH correlated significantly with the dose of vitamin D in groups 1 and 3: 0.13 ± 0.19 μ g/kg daily (range: 0.01–0.1 μ g/kg) versus 0.42 ± 0.35 μ g/kg daily (range: 0.14–1.03 μ g/kg) respectively, $p < 0.05$.

We observed no significant differences between the three groups in values for plasma calcium. Mean plasma calcium values at months 1, 6, and 12 for group 1 were 10 ± 1.02 mg/dL, 10.5 ± 0.5 mg/dL, and 10.6 ± 0.35 mg/dL respectively; for group 2, they were 9.1 ± 0.42 mg/dL and 9.4 ± 0.76 mg/dL at months 1 and 6 respectively; and for group 3, they were $10.10 \pm$

TABLE I Age, sex, and time on dialysis for the study groups

	All patients (n=20)	1 (n=12)	Groups	
			2 (n=2)	3 (n=6)
Age (years)	5.8 ±5 (0.2–14.8)	6.2±5 (0.2–14.83)	7.2±8.7 (1.1–13.2)	4.8±5.2 (1.1–14.6)
Sex (M/F)	12/8	7/5	1/1	4/2
Time PD (months)	11.2±14.1 (0–46)	16.9±15.8 (0–46) ^b	2±1.41 (1–3)	2.8±3.8 (0–9) ^b

^a *p* = nonsignificant.

^b *p* < 0.05.

M/F = male/female; PD = peritoneal dialysis.

TABLE II Biochemical variables at months 1, 6, and 12 for groups 1, 2, and 3

	All patients			Group 1			Group 2			Group 3		
	1	6	12	1	6	12	1	6	12	1	6	12
Patients (n)	20	20	9	12	12	4	2	2	0	6	6	5
Z T/E	-2.38	-2.37	-2.29	-2.38	-2.26	-2.15	-3.22	-3.44	—	-2.09	-2.21	-2.37
Kt/V	3.3	3.4	3.5	3.6 ^a	3.27	3.4	1.9 ^a	3.5	—	3.4	3.6	3.6
nPNA	1.4	1.5	1.5	1.4	1.5	1.4	0.9	1	—	1.3	1.5	1.6
iPTH	423.7	291.6	616.4	52	163	171.5	208.5	306.1	—	1239	544	972
Vitamin D ^b	0.21	0.18	0.2	0.13 ^a	0.08 ^a	0.10 ^a	0.1	0.25	—	0.42 ^a	0.37 ^a	0.27 ^a
Serum Ca	9.9	10.2	10.4	10	10.5	10.6	9.1	9.6	—	10.1	9.8	10.2
Serum phosphorus	4.7	4.6	5.2	4.76	4.42	4.08 ^a	4.5	5.2	—	4.5	4.8	5.8 ^a
Ca × P	46.4	47.2	43.7 ^a	47.6	47.1	43.7	40.6	49.1	—	45.2	46.7	59.2 ^a
Albumin	3.5	3.7	3.9	3.4 ^a	3.6	3.8	3.7	3.8	—	3.7 ^a	3.8	3.7
Hemoglobin	10.7	11.3	9.5	11.4	11.5	10.9	9.6	12.8 ^a	—	9.6	10.4 ^a	8.5
Serum ferritin	288	209	382	285	178 ^a	126 ^a	107	32.7 ^a	—	319	351 ^a	535 ^a
pH	7.37	7.37	7.36	7.38	7.37	7.39	7.35	7.3	—	7.37	7.36	7.35
Bicarbonate	24.7	23.8	23.4	25.4	24.3	25.7	23	21.5	—	23.7	23.1	22.1

^a *p* < 0.05.

^b Daily dose of vitamin D in µg/kg.

Z T/E = Z score for height/age; nPNA = normalized protein equivalent of nitrogen appearance; iPTH = intact parathyroid hormone.

0.26 mg/dL, 9.75 ± 1.12 mg/dL, and 10.18 ± 0.69 mg/dL respectively (range: 9.7 – 11.3 mg/dL).

Phosphorus levels at months 1, 6, and 12 for group 1 were 4.76 ± 1.65 mg/dL, 4.42 ± 0.92 mg/dL, and 4.08 ± 1.05 mg/dL respectively; for group 2, the values were 4.45 ± 0.35 mg/dL and 5.15 ± 0.35 mg/dL at months 1 and 6 respectively; and for group 3, they were 4.48 ± 0.69 mg/dL, 4.82 ± 0.88 mg/dL, and 5.82 ± 0.83 mg/dL respectively (*p* = nonsignificant).

The values for Ca × P at months 1, 6, and 12 for group 1 were 47.6 ± 18.4, 47.1 ± 9.6, and 43.7 ± 14.9 respectively; for group 2, they were 40.6 ± 5.11 and 49.1 ± 0.63 at months 1 and 6 respectively; and for group 3, they were 45.2 ± 6.6, 46.7 ± 8, and 59.2 ± 9.2 respectively. The difference between group 1 and group 3 at 12 months was statistically significant (*p* > 0.05). At the end of the first year, the mean value for

Ca × P in group 3 surpassed the level recommended in the DOQI guidelines.

At the beginning of our study, the Z score for height was -2.38 ± 1.31 (range: -4.75 to -0.3). By month 12 of follow-up, the score was -2.29 ± 1.62 (range: -4.88 to 0.43), with a nonsignificant difference between the groups (*p* = 0.44).

At months 1, 6, and 12, the mean dialysis dose in the patients, measured as Kt/V, was 3.3 ± 1.1, 3.4 ± 1.26, and 3.5 ± 1.47 respectively. At month 1, group 2 had a lower Kt/V than group 1 did: 1.9 ± 0.21 versus 3.6 ± 0.98, *p* < 0.05. At months 1, 6, and 12, nPNA was 1.4 ± 0.45 g/kg/day, 1.5 ± 0.3 g/kg/day, and 1.5 ± 0.3 g/kg/day respectively, with no differences between the three groups. Albuminemia mean values for months 1, 6, and 12 were 3.5 ± 0.3 mg/dL, 3.7 ± 0.4 mg/dL, and 3.9 ± 0.3 mg/dL respectively, with no

differences between the groups. Plasma pH and plasma bicarbonate showed no statistically significant difference between the groups.

At the end of the follow-up period, ferritin values in group 3 were significantly higher than those seen in group 1 (535 ± 304.9 mg/dL vs. 125.7 ± 98.7 mg/dL, $p < 0.05$), but the higher values were not associated with higher hemoglobin or hematocrit values.

When we analyzed the various variables, searching for correlations between them, we found that the vitamin D dose correlated positively with the iPTH logarithm ($r = 0.43$, $p < 0.01$). The same correlation was observed between the iPTH logarithm and plasma levels of alkaline phosphatase ($r = 0.56$, $p < 0.01$). However, when we reallocated the study patients into two groups (plasma iPTH lower or higher 700 pg/mL), the positive correlation between iPTH logarithm and alkaline phosphatase was lost ($p > 0.05$).

Discussion

Peritoneal dialysis has been widely accepted as the predominant mode of dialysis in children with chronic renal failure, but persistent bone disease remains a major problem in the clinical management of pediatric patients (19). In pediatrics, secondary hyperparathyroidism was observed to be the predominant skeletal lesion, but in recent years low-turnover bone disease has been observed more frequently (13,20,21).

Low-turnover disease represents a major challenge to nephrologists, probably because it represents an acquired lesion, secondary to a number of therapeutic interventions. Defective mineralization of osteoid leads to osteomalacia in adults and rickets in children, with a delay in the rate of bone mineralization that finally results in accumulation of excess unmineralized osteoid (7). Pediatric patients show bone pain, walking disturbances, skeletal deformities, fractures, and—most important—growth retardation. Osteomalacia has usually been associated with aluminum overload in adults (13,20,22), but several mechanisms may underlie the disorder: for example, a relative or absolute deficiency of vitamin D or its active metabolites, or a peripheral resistance to their action; and high magnesium content in the bone of such patients, which interferes with the process of normal mineralization or maturation of amorphous calcium phosphate to its crystalline phase. Magnesium stabilizes amorphous calcium phosphate and inhibits its transformation into hydroxyapatite crystals (1,10).

The other histopathologic type of low-turnover bone disease is the adynamic form, with a reported prevalence between 15% and 60% in dialysis patients. The exact mechanisms underlying adynamic lesions are not fully elucidated. They are characterized by a defect in bone matrix formation and mineralization, increased osteoid thickness, and reduced numbers of osteoblast and osteoclast cells alike (2,3,9). Dialysis patients with adynamic bone disease have lower blood levels of iPTH than do their counterparts, secondary to oversuppression of parathyroid gland activity by high calcium intake, overtreatment with 1,25-dihydroxyvitamin D₃, and, in the adult population, diabetes and aluminum overload.

According to the DOQI guidelines, serum iPTH levels less than 100 pg/mL reliably predict the presence of adynamic bone disease, and iPTH levels greater than 500 pg/mL are frequently associated with high-turnover disease (10). We used cut-off values of 150 pg/mL and 400 pg/mL to represent low-turnover and high-turnover disease respectively, unless a patient with a level between those limits showed unexplained hypercalcemia or an acute increase in alkaline phosphatase activity.

Given our criteria, 60% of our patients showed low-turnover disease, and 30% showed high-turnover disease. The other 10% could be considered within the “safe” limits of iPTH (“controlled” ROD). Our results are similar to those of Sanchez *et al.*, who found 63.3% adynamic lesions, and to those of Goodman *et al.* (21), who reported an incidence of 40% of low-turnover bone disease.

In our country, during the mid 1990s, high-turnover bone disease was frequently found in children on PD and hemodialysis. Our group (16) described 9 patients with this kind of bone lesion—all of them with high levels of iPTH.

The current increase in low-turnover disease might be the result of several factors, such as the availability of calcitriol treatment and calcium therapy (20). Still, most patients at the beginning of their disease show high-turnover bone disease, with high plasma levels of iPTH and enhanced numbers and activity of osteoclasts, leading to increased bone resorption (1,23).

When we compared mean iPTH values in patients on PD for less than 6 months before entering our study with those in patients who had been receiving PD for more than 6 months, we found that the former group

had the higher iPTH levels (629.13 pg/mL vs. 115.53 pg/mL, $p = 0.04$). As well, group 1 patients (iPTH values < 150 pg/mL) had been maintained significantly longer on PD before entering the study than had the group 3 patients.

The mean iPTH value observed in group 1 was 52 pg/mL. That group therefore received a lower dose of 1,25-dihydroxyvitamin D₃ (0.13 µg/kg weekly) as compared with group 3, who had a mean iPTH value of 1239 pg/mL and who received a vitamin D dose of 0.42 µg/kg weekly ($p < 0.05$). This last group showed a marked decrease (57%) in iPTH level at 6 months' follow up. At that time, the vitamin D dose was reduced in 27% of patients, with the consequence that we observed an increase in iPTH value (which did not, however, reach initial values). That finding once again shows how difficult it is to manage ROD in children.

When patients proved to be resistant to daily oral treatment with the active form of vitamin D, we used others protocols, including administration of oral pulses of vitamin D [large intermittent doses 2 – 3 times per week (16)].

Some authors have reported successful experiences with intraperitoneal or intravenous doses of vitamin D in pediatric uremic patients. Salusky *et al.* and other investigators (4,17,24) reported on 46 pediatric patients on continuous cycling PD treated with oral (PO) or intraperitoneal (IP) calcitriol. After 9 months of therapy, the IP group showed a decrease in iPTH level to 169 ± 57 pg/mL from 648 ± 125 pg/mL. The group treated with PO calcitriol showed no change from the baseline iPTH level. However, both groups showed an improvement in the skeletal lesions of secondary hyperparathyroidism, and 33% of the patients developed adynamic bone lesions. Those results clearly show how difficult the follow-up of patients treated for high-turnover bone disease can be when iPTH plasma levels are used to guide the therapy. In our experience, iPTH levels decreased in 4 of 6 patients after 6 months of treatment. However, in patients who completed 12 months of follow-up ($n = 3$), that tendency was lost, and iPTH levels returned to initial values.

We need to trust PTH levels in the absence of a bone biopsy for accurate diagnosis of ROD, but most of the currently used PTH assays measure only the "intact" molecule, consisting of 84 amino acids. However, most of the biological activity of PTH is local-

ized in the N terminal, and iPTH assays also detect biologically inactive fragments of PTH that are retained in CRF but are far from that portion of the molecule (amino acids in the 7th – 84th position). The result could be an overestimation of actual PTH levels, leading to confusion when correlations between biochemical and histologic results are made. Newer PTH assays are currently being used to correct that bias.

The DOQI guidelines have analyzed another point that deserves attention in the treatment of dialyzed patients. In patients who have not received calcitriol therapy, or in those who have received "regular" oral doses lower than 0.5 µg daily, serum levels of iPTH correlate well with the degree of secondary hyperparathyroidism. However, the use of large, intermittent doses of active vitamin D can disrupt the relationship between plasma iPTH levels and the rates of bone formation and turnover in those patients (17). In addition, the linear correlation between the iPTH logarithm and alkaline phosphatase ($r = 0.56$, $p < 0.01$) appears to be lost when patients with iPTH levels over 700 pg/mL ($p > 0.05$) are treated, suggesting that alkaline phosphatase is no longer helpful for patients with iPTH values over 700 pg/mL.

In end-stage renal disease, lifespan is reduced. One of the major causes of morbidity and mortality in the patients is cardiovascular disease, and epidemiologic studies have emphasized the contributory roles of phosphorus and calcium.

As renal insufficiency advances, hyperphosphatemia becomes a common problem. In the United States, nearly 40% of hemodialysis patients have phosphatemia greater than 6.5 mg/dL (25). Hyperphosphatemia activates synthesis of mRNA of proteins related to osteogenesis—such as osteocalcin and Bfa1—in the smooth muscle cells of the coronary blood vessels (26), leading to the calcifications found in the intima and media layer of those arteries in patients older than 18 years (27).

Hypocalcemia is the consequence of the poor renal dihydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, its active form, which is able to maintain normal calcium levels by means of adequate intestinal calcium absorption, bone mineralization, and plasma levels of parathormone. Correction of hypocalcemia and hypophosphatemia are achieved by exogenous administration of vitamin D

or calcium-containing phosphorus binders. However, such therapy also leads to an increase in intestinal phosphorous absorption and high levels of calcemia, and a positive calcium and phosphorous balance has been associated with high levels of mortality (25,28). In recent years, new phosphate binders have been developed. One of these, sevelamer, is a non calcium, non aluminum-containing hydrogel, which has the property of non absorption from the gastrointestinal tract (29). Patients with phosphorous levels greater than 6.5 mg/dL and $\text{Ca} \times \text{P}$ greater than 72 mg/dL have higher mortality rates than do patients with lower phosphorous levels and $\text{Ca} \times \text{P}$ less than 52 mg/dL. In recent years, hyperphosphatemia, coronary artery calcification, and calciphylaxis have emerged as the main consequences of ROD and its treatment (6,22).

The DOQI guidelines recommend maintaining calcium levels between 9.5 mg/dL and 10.2 mg/dL, phosphorus levels between 5.5 mg/dL and 6 mg/dL, and $\text{Ca} \times \text{P}$ below 55 mg/dL (10). In our results, we found no differences in calcium, phosphorus, or $\text{Ca} \times \text{P}$ between the study groups. However, we did find that, in group 3 patients, at the end of 12 months of follow up, the mean $\text{Ca} \times \text{P}$ value was above the value recommended by the DOQI guidelines, increasing the cardiovascular risk for those patients. The higher vitamin D doses administered to those patients could be the explanation for the difference.

High levels of PTH contribute to resistance to recombinant human erythropoietin (30), but when we analyzed the hemoglobin levels in our study groups, we were surprised to find no differences between them. However, ferritin levels were higher in group 3 than in groups 1 and 2.

Conclusion

Renal osteodystrophy is frequently found in pediatric patients on PD, but it remains a problem without a solution. To date, no published study can tell us how much and how long we need to treat ROD with vitamin D in pediatric PD patients, without an increased risk for morbidity and mortality. New multicenter, controlled, prospective trials are needed to develop a protocol for ROD treatment in pediatrics.

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Nitrogen Balance Studies and Kt/V Urea in Children Undergoing Chronic Peritoneal Dialysis

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Currently, urea kinetic modeling has been accepted for the routine evaluation of peritoneal dialysis (PD) through the calculation of Kt/V (normalized whole body urea clearance) and nPNA (normalized protein equivalent of total nitrogen appearance). In pediatric dialysis, the exact meaning of, and target values for, those parameters is still under debate.

We evaluated the mean values and correlations between Kt/V urea and parameters of nutrition. During a 12-month period, we prospectively performed 186 nitrogen balance studies in pediatric patients on chronic PD. We also assessed daily protein intake (DPI) by nutritional evaluation. Protein, albumin, urea, and creatinine were analyzed in dialysate and urine, collected once monthly. Dialysis adequacy was evaluated using monthly measurements of Kt/V urea and creatinine clearance (CCr) in urine and dialysate. All statistical comparisons were performed using the paired t-test. Two-way analysis of variance for repeated measures was used to calculate correlations. A p value less than 0.05 was considered significant.

We studied 20 patients (15 boys, 5 girls) of mean age 5.1 ± 4.7 years (range: 3 months – 14.8 years). Mean DPI in these patients was 3.52 ± 1.1 g/kg/day. Weekly total Kt/V urea was 3.41 ± 1.35 , and residual Kt/V urea was 1.69 ± 1.46 . Weekly total and residual CCr were 72.4 ± 70 L and 45 ± 44 L respectively. Mean protein catabolic rate (PCR) was 0.84 ± 0.33 g/kg/day, showing a net nitrogen balance (NB = DPI – PCR) of $+1.37 \pm 0.4$ g/kg/day. The mean nPNA was 1.38 ± 0.40 g/kg/day, with positive correlations with DPI, PCR, and total Kt/V ($p < 0.001$). Total Kt/V showed significant positive correlations with PCR ($p <$

0.001) and nPNA ($p < 0.001$), but not with NB ($p = 0.23$) and DPI ($p = 0.21$). A negative correlation was found between all urea kinetic parameters and plasma bicarbonate ($p < 0.001$).

The values of Kt/V urea and nPNA in our patients were higher than those recommended in the adult literature. The positive correlations seen between Kt/V urea and nPCR and nPNA could not be demonstrated between Kt/V and DPI or NB, suggesting that the correlations could be the result of a mathematical association. The negative correlations between plasma bicarbonate and urea kinetic variables suggest a negative impact of acidosis on nutrition status in our patients.

Key words

Urea kinetic modeling, Kt/V urea, protein equivalent of total nitrogen appearance, protein catabolic rate, dietary protein intake

Introduction

During the last 30 years, urea kinetic modeling (UKM) has been routinely used to adjust dialysis therapy. The National Cooperative Dialysis Study (NCDS) in adult hemodialysis (HD) patients in the early 1970s was the first attempt at providing parameters of adequacy (1). Currently, UKM is widely used to manage chronic peritoneal dialysis (PD) patients, especially by measuring dialysis dose (Kt/V), protein catabolic rate (PCR), and protein equivalent of total nitrogen appearance (PNA) according to the guidelines (2) set out by the Dialysis Outcomes Quality Initiative (DOQI).

Therapy supervision by UKM has gained popularity because, in the adult PD population, a strong association with morbidity and mortality has been described for Kt/V and nutrition, and also because PCR and PNA are closely related to daily protein intake (DPI). The CANUSA study (3) in adults reported

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a 5% decrease in patient survival associated with every 0.1 decrease in total weekly Kt/V urea for Kt/V values between 1.5 and 2.3.

In pediatrics, the Mid-European Pediatric Peritoneal Dialysis Study Group (4) showed a significant positive effect of creatinine clearance (CCr) on the change in height standard deviation score (SDS), and Holtta *et al.* (5) found an accelerated height velocity in 62% of patients who met or exceeded the DOQI recommendations for small-solute clearance. A weekly Kt/V urea equal to or greater than 2 is proposed as the “gold standard” by the DOQI guidelines (6), and that value approximates a renal creatinine clearance of 9–14 mL/min/1.73 m². For pediatric patients, the DOQI Work Group suggests that the target dialysis dose should always meet or exceed the adult recommendations.

The NCDS (1) also showed PCR to be a determinant of good outcome, and better survival has been reported (7) in PD patients with a high PNA normalized to body weight (nPNA). According to DOQI recommendations, the goal is to achieve an nPNA of at least 0.9 g/kg/day in adult PD patients. No target value has been established for children, however.

In recent years, published experiences have settled some of the doubts about the validity of UKM parameters in terms of long-term patient outcome. Maiorca *et al.* (8) showed that indices of adequacy were predictors of mortality and morbidity in both continuous ambulatory peritoneal dialysis (CAPD) and HD, whereas PCR normalized to body weight (nPCR) and subjective global assessment of nutrition status were not. The ADEMEX trial (9) examined the effect of increased small-solute clearances on patient mortality. Death was the primary endpoint of the study, and nutrition status evaluated by PNA was a secondary endpoint. After 2 years of follow-up, the mortality rates for patients with normal and high small-solute clearances were the same, even when the patients were stratified by other variables such as nPNA. In that trial, a PNA value of 0.8 g/kg/day was found to be critical for patient survival.

Beyond those contradictory data, PD prescription in children is still largely empirical. The effects of dialysis adequacy on patient survival and nutrition status have not been clearly assessed, and the correlation between UKM and clinical outcome is still under debate. The exact values of Kt/V, PCR, and PNA needed in children are unknown, mainly because the

interest in efficacy questions related to pediatric PD adequacy is limited (10–16). The underlying reasons are the high patient turnover in pediatric PD, the relatively short dialysis periods, and the low morbidity and mortality rates, which are chiefly secondary to associated pathologies rather than to dialysis insufficiency (17). The ever-changing nutrition (and therefore dialytic) requirements from neonate to adolescent present a great challenge to pediatric nephrologists, and recommending specific values for Kt/V and PNA in pediatric PD is still not possible.

In the present study, we evaluated the relationships between dialysis dose, Kt/V, and parameters of nutrition [PCR, nitrogen balance (NB), and PNA] in pediatric patients on chronic PD.

Patients and methods

Between April 2001 and September 2003, we undertook a prospective, controlled study at the Luis Calvo Mackenna Children’s Hospital, Pediatric Division, University of Chile. We evaluated 20 stable children on chronic outpatient PD therapy. Mean time on PD at time of enrollment into the study was 9 months (range: 2–23 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.

During a 12-month follow-up period, we measured peritoneal and residual Kt/V, peritoneal and urinary urea nitrogen, DPI, and albumin and total protein losses monthly.

Calculations

We calculated Kt/V urea as

$$\text{Kt/V urea} = [24\text{-h dialysate volume (L)} \\ \times \text{D/P urea} \times 7] / [0.60 \times \text{weight (kg)}].$$

Dialysis dose was prescribed considering the minimum weekly value of 2 recommended in the DOQI

guidelines (2), but no attempt was made to define a maximum Kt/V value.

We derived the PCR from daily urea generation (in grams) or urea nitrogen appearance (UNA), which is the net production or appearance of urea nitrogen in body fluids. For patients undergoing CAPD, UNA has been calculated as follows:

$$\text{UNA (g/day)} = [(V_d \times \text{dUN}) + (V_u \times \text{uUN})] \times t$$

where V_d and V_u are the dialysate and urine volumes respectively (in liters), dUN and uUN are dialysate and urine concentrations of urea nitrogen (in grams per liter), and t is the duration of fluid collection, typically 24 hours (1 day). In the dialysis literature (18), DPI estimated from UNA has been called the “protein catabolic rate,” and PCR is calculated according to the formula

$$\text{PCR (g/kg/day)} = [(\text{uUNA} + \text{dUNA}) \times 6.25] / \text{weight (kg)}$$

where uUNA is the urinary nitrogen appearance and dUNA is the dialysate nitrogen appearance. However, although PCR is a useful concept, we believe that the term is misleading. Intact proteins, peptides, and amino acids lost in dialysate and urine comprise a portion of the PCR, but they are not catabolized to urea. The new term PNA was therefore introduced a few years ago. Its advantage is that it describes more correctly the metabolic processes that it represents. We used the Borah equation to calculate the PNA according to DOQI guidelines:

$$\text{PNA (g/day)} = (6.49 \times \text{UNA}) + (0.294 \times V) + \text{protein losses (g/day)}$$

where UNA is total urea nitrogen appearance (urine and dialysate) in grams per day. The nPNA is the PNA value normalized to a kilogram of body weight.

Nutrition

A renal dietician evaluated the study patients monthly to assure adequate protein and energy intake according to the pediatric recommended dietary allowances (19). A weekly nutritional follow-up was performed by telephone to correct any deviations from the protocol. Anthropometric development was evaluated using weight, height, and body mass index. Height

was measured in the supine position for every patient younger than 2 years old. For the remaining patients, a stadiometer was used. All growth measurements are expressed as standard deviation score (SDS, Z), derived from published data. All patients, without exception, were fed through a nasogastric tube or gastrostomy to assure the desired intake.

Nitrogen from unmeasured respiratory, intestinal, and dermal losses are not included in routine measurements of PNA and PCR—a situation that affects the results of balance studies. To estimate the total protein catabolism and losses in clinical practice, we use the sum of PCR, plus albumin losses in urine and dialysate, plus unmeasured losses, so that the daily protein catabolism (DPC) in grams was calculated to be

$$\begin{aligned} \text{DPC} = [& \text{UNA}_d (24 \text{ h}) \times 6.25] + [\text{UNA}_u (24 \text{ h}) \\ & \times 6.25 \times 1.25] + \text{Alb}_d (24 \text{ h}) + \text{Alb}_u (24 \text{ h}) \\ & + [\text{weight (kg)} \times 0.045 \times 6.25]. \end{aligned}$$

We recorded DPI minus DPC (g/day) as NB.

Statistical analysis

Data are reported as mean \pm standard error. All statistical comparisons were performed using the paired t -test and multiple linear regression analysis. The two-way analysis of variance for repeated measures was used to calculate correlations, and a p value less than 0.05 was considered significant.

Results

We performed 186 laboratory measurements in the 20 study patients (15 boys, 5 girls; mean age: 5.1 \pm 4.7 years; age range: 3 months – 14.8 years). Total and residual Kt/V urea were 3.41 \pm 1.35 and 1.69 \pm 1.4 respectively. Weekly CCr was 72.4 \pm 70 L (residual) and 45 \pm 44 L (peritoneal). Mean daily protein intake was 3.49 \pm 1.1 g/kg, mean daily peritoneal and urinary albumin losses were 136 \pm 86 mg/kg and 27.5 \pm 41 mg/kg respectively, and total daily peritoneal protein losses were 12.34 \pm 8.1 g/day. Mean PCR was 0.84 \pm 0.33 g/kg/day, and mean nPNA was 1.36 \pm 0.40 mg/kg/day. Mean daily NB was 1.37 \pm 0.40 g/kg, a value close to the mean nPNA result obtained using the Borah equation (2). Table I summarizes the results.

Total Kt/V showed a significant positive correlation with PCR ($r = 0.45$, $p < 0.001$) and with nPNA

TABLE I Urea kinetic variables in 20 children on peritoneal dialysis

Residual Kt/V urea (L/week)	1.69±1.4
Total Kt/V urea (L/week)	3.41±1.35
Protein intake (g/kg/day)	3.49±1.1
Protein catabolic rate (g/kg/day)	0.84±0.33
nPNA (g/kg/day)	1.36±0.40
Nitrogen balance (g/kg/day)	1.37±0.40

nPNA= protein equivalent of urea nitrogen appearance.

($r = 0.49$, $p < 0.001$), but not with NB ($p = 0.23$) and DPI ($p = 0.21$; Table II). When the study patients were allocated to groups according to Kt/V value, 10 patients had a weekly Kt/V < 3 (mean: 2.52 ± 0.23), and 10 patients had a weekly Kt/V > 3 (mean: 4.26 ± 0.74). In the “low” Kt/V group, the mean nPNA was 1.22 ± 0.27 g/kg, the mean PCR was 0.74 ± 0.21 g/kg, and the mean DPI was 2.96 ± 1.03 g/kg. In the “high” Kt/V group, those values were 1.49 ± 0.25 g/kg, 0.93 ± 0.22 g/kg, and 3.79 ± 0.84 g/kg respectively, all statistically significant ($p < 0.05$). However, when urea kinetic variables were evaluated for both groups, the correlation between dialysis dose and PCR and nPNA became stronger for patients with a weekly Kt/V < 3 ($r = 0.76$ and $r = 0.84$ respectively, $p < 0.001$), and they became non-significant for patients with a weekly Kt/V > 3 ($r = 0.154$ and 0.159 respectively, $p > 0.05$).

The patients' DPI was positively correlated with PCR and nPNA ($p < 0.001$) and also with residual Kt/V, but no correlation was observed with total Kt/V.

A strong negative correlation was found between all urea kinetic parameters (Kt/V, DPI, PCR, PNA) and plasma bicarbonate. No correlation was found between albumin level and Kt/V, PCR, or nPNA.

TABLE II Urea kinetic correlation studies in 20 children on peritoneal dialysis

	r^2	p Value
Total Kt/V urea vs. nPCR	0.45	<0.001
Total Kt/V urea vs. nPNA	0.49	<0.001
Total Kt/V urea vs. NB	0.23	NS
Total Kt/V urea vs. DPI	0.21	NS
DPI vs. nPCR	0.44	<0.001
DPI vs. nPNA	0.52	<0.001

Kt/V = dialysis dose; nPCR = normalized protein catabolic rate (g/kg/day); nPNA = normalized protein equivalent of urea nitrogen appearance (g/kg/day); NB = nitrogen balance (g/kg/day); DPI = daily protein intake (g/kg/day).

Discussion

The management of dialyzed children should certainly be based more on overall clinical and laboratory parameters than on urea kinetic modeling; however, UKM is widely used to manage adult and pediatric patients in an attempt to find a “short way” to achieve the best clinical outcome on PD therapy (6–14). The best clinical outcome should be the lowest morbidity and mortality in adult patients and the best growth in pediatric patients. Despite the generalized use of Kt/V and its significant correlations with parameters of nutrition such as PCR and nPNA, the exact value of the urea kinetic measurements required to achieve positive growth in children are currently a matter of debate (11–14).

Based on accepted, published adult experiences, the weekly minimum delivered dialysis dose (target Kt/V urea) is 2.0 (2,3), and the weekly minimum target CCr is 60 L/1.73 m². The data are insufficient to address the issue of adequate versus optimal dialysis dose, and therefore the minimum Kt/V recommended by DOQI does not resolve the question of what is the best dose for dialyzed patients. A PNA of at least 0.9 g/kg/day in adult PD patients has been suggested as a target by the DOQI guidelines (2).

Pediatric studies have found higher mean values for Kt/V and PNA than are seen in adults. Schaefer *et al.* (12) reported a mean Kt/V of 2.3 ± 0.89 (range: 1–4.41), Holtta *et al.* (5) demonstrated a Kt/V of 3.2 ± 0.5 , and Chadha *et al.* (20) reported a mean Kt/V of 3.39 ± 0.71 . Values for PNA have been measured at 1.46 ± 0.24 g/kg/day by Aranda *et al.* (14) and 1.08 ± 0.61 g/kg/day (range: 0.4–3.37 g/kg/day) by the Mid-European Pediatric Peritoneal Dialysis Study Group (4). The mean total Kt/V urea for our group of 20 patients was 3.41 ± 1.35 , perhaps reflecting the residual Kt/V value of 1.69 ± 1.4 . As expected, our nPNA results were also higher than those for adults patients (1.36 ± 0.40 mg/kg/day), and both kinetic parameters showed a significant association with the high DPI observed during the study (3.52 ± 1.1 g/kg/day).

The high correlations between Kt/V urea and all indices of nutrition have frequently been observed in various studies (4,11,12,21,22) since the first report from NCDS (23), in which the midweek predialysis BUN, PCR, and Kt/V were shown to be mathematically interrelated. Our results show the same sustained positive association between dialysis dose (Kt/V) and PCR and nPNA, but not between dialysis dose and

DPI or NB. The positive correlation between Kt/V and PNA may indicate increased dietary protein intake in patients with increased appetite as dialysis dose increases (11), but it may simply reflect the fact that nPNA and Kt/V are mathematically linked (being calculated from the same initial variables). According to our results (derived from 186 measurements in 20 patients, with a monthly recorded DPI), better Kt/V does not mean a better DPI or NB as has been proposed (11,12,24), but dialysis dose nevertheless correlates highly with nPCR and nPNA. That question—which comes first: Kt/V or PCR (chicken or egg)—was highlighted by Lindsay *et al.* (25), who studied 30 HD and 9 PD adult patients, finding evidence that PCR depends on the Kt/V urea in HD patients and that, in PD patients who receive a higher dose of dialysis, PCR increases 3 months after the change in Kt/V. The data suggest that changes in Kt/V urea are followed by changes in PCR, but they still do not answer the original question: Is it a matter of a mathematical or a clinical relationship?

Schaefer *et al.* (12) reported on 43 children on CAPD and 42 on continuous cycling PD (CCPD). The children were similar in age, body size, duration of dialysis, underlying disease, and residual renal function. Average serum creatinine and BUN values were similar in both groups. In patients treated with CCPD as compared with CAPD patients, Kt/V urea was significantly higher, as was PCR (1.39 ± 0.6 g/kg/day vs. 1.08 ± 0.48 g/kg/day, $p < 0.05$). When we divided our study population into groups with a weekly Kt/V less than or greater than 3, we found the same differences in nPNA, nPCR, and DPI between the two groups as Schaefer did: high values for the high Kt/V group, and lower values for the low Kt/V group. Those authors concluded that the greater PCR and DPI suggested better control of anorexia with CCPD (higher Kt/V) than with standard CAPD (lower Kt/V). However, when we evaluated our results separately for each group, the low Kt/V group showed a high relationship with indices of nutrition, while that correlation was lost in the high Kt/V group.

The mean nPNA in our study group was 1.36 ± 0.40 mg/kg/day, quite similar to that of the CCPD group reported by Schaefer *et al.*; however, the DPI was different [1.49 ± 0.86 g/kg (Schaefer) vs. 3.49 ± 1.1 g/kg (our group)]—a difference that can be explained by the mean age of the patients [11.4 ± 5.7 years (Schaefer CCPD group) vs. 5.1 ± 4.7 years (our patients)]. In our

experience, the correlation between age and DPI is strongly negative ($r = -0.83$, $p < 0.001$).

Conclusion

Our preliminary data provide evidence for a correlation between small-solute clearance and kinetic parameters of nutrition, suggesting that those results could be a mathematical association. The exact meaning of those findings for the outcome of pediatric patients on chronic PD remains to be elucidated. Because mortality is an uncommon outcome in the pediatric end-stage renal disease population, growth could potentially serve as an outcome measure. To try to find the Kt/V urea and nPNA associated with the best growth, we are incorporating more patients into our 12-month follow-up protocol.

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