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The bone and mineral disorder of children undergoing chronic peritoneal dialysis

Dagmara Borzych[1,2], Lesley Rees[3], Il Soo Ha[4], Annabelle Chua[5], Patricia G. Valles[6], Maria Lipka[7], Pedro Zambrano[8], Thurid Ahlenstiel[9], Sevcan A. Bakkaloglu[10], Ana P. Spizzirri[11], Laura Lopez[12], Fatih Ozaltin[13], Nikoleta Printza[14], Pankaj Hari[15], Günter Klaus[16], Mustafa Bak[17], Andrea Vogel[18], Gema Ariceta[19], Hui Kim Yap[20], Bradley A. Warady[21] and Franz Schaefer[1], for the International Pediatric PD Network (IPPN)[2]

[1]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany; [2]Department of Pediatric Nephrology, Medical University of Gdansk, Gdansk, Poland; [3]Nephrology Department, Great Ormond Street Hospital for Children NHS Trust, London, UK; [4]National University Children's Hospital, Dialysis Center for Children and Adolescents, Seoul, South Korea; [5]Dialysis Unit, Texas Children's Hospital, Houston, Texas, USA; [6]Hospital Pediatrico Humberto Notti, Mendoza, Argentina; [7]Department of Nephrology, Kidney Transplantation and Arterial Hypertension, Children's Memorial Hospital, Warsaw, Poland; [8]Hospital Dr Exequiel Gonzalez Cortes, Santiago, Chile; [9]Medizinische Hochschule, KfH Pediatric Kidney Center, Marburg, Hannover, Germany; [10]Department of Pediatric Nephrology, Gazi University Hospital, Ankara, Turkey; [11]Servicio de Nefrología Hospital de Niños Sor María Ludovica, La Plata, Argentina; [12]Department of Pediatric Nephrology, Hospital de Pediatría Garrahan, Buenos Aires, Argentina; [13]Department of Pediatric Nephrology, Hacettepe University, Ankara, Turkey; [14]Pediatric Nephrology Unit, Aristoteles University, Thessaloniki, Greece; [15]All India Institute of Medical Sciences, New Delhi, India; [16]KfH Pediatric Kidney Center, Marburg, Germany; [17]Dr Behcet Uz Children Research and Education Hospital, Izmir, Turkey; [18]Department of Pediatrics, Pontificia Universidad Católica de Chile, Santiago, Chile; [19]Hospital de Cruces, Baracaldo, Spain; [20]Shaw-NKF-NUH Children's Kidney Centre, Singapore, Singapore and [21]Dialysis and Transplant Section, Children's Mercy Hospital, Kansas City, Missouri, USA

The mineral and bone disorder of chronic kidney disease remains a challenging complication in pediatric end-stage renal disease. Here, we assessed symptoms, risk factors and management of this disorder in 890 children and adolescents from 24 countries reported to the International Pediatric Peritoneal Dialysis Network Registry. Signs of this disease were most common in North American patients. The prevalence of hyperphosphatemia increased with age from 6% in young infants to 81% in adolescents. Serum parathyroid hormone (PTH) was outside the guideline targets in the majority of patients and associated with low calcium, high phosphorus, acidosis, dialysis vintage and female gender. Serum calcium was associated with dialytic calcium exposure, serum phosphorus with low residual renal function and pubertal status. PTH levels were highest in Latin America and lowest in Europe. Vitamin D and its active analogs were most frequently administered in Europe; calcium-free phosphate binders and cinacalcet in North America. Clinical and radiological symptoms markedly increased when PTH exceeded 300 pg/ml, the risk of hypercalcemia increased with levels below 100 pg/ml, and time-averaged PTH concentrations above 500 pg/ml were associated with impaired longitudinal growth. Hence, the symptoms and management of the mineral and bone disorder of chronic kidney disease in children on peritoneal dialysis showed substantial regional variation. Our findings support a PTH target range of 100–300 pg/ml in the pediatric age group.

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The management of the mineral and bone disorder (MBD) associated with chronic kidney disease (CKD–MBD) is particularly challenging in children and adolescents with end-stage renal disease (ESRD), in whom treatment efforts not only need to prevent debilitating musculoskeletal morbidity but also must be compatible with statural growth and, in view of a potentially long lifespan, consider preservation of long-term cardiovascular health. In this context, the optimal target concentration ranges of parathyroid hormone (PTH) and mineral electrolytes allowing appropriate bone turnover and avoiding extraosseous calcifications are a focus of attention. Current pediatric consensus guidelines recommending permissive mild-to-moderate hyperparathyroidism (HPT) and maintenance of low normal serum calcium (Ca) and normal inorganic phosphorus (Pi) levels operate on a limited evidence base.[1,2,3]

Recently, the International Pediatric Peritoneal Dialysis Network (IPPN) established a prospective clinical registry collecting detailed clinical and biochemical information in

Correspondence: *Franz Schaefer, Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Im Neuenheimer Feld 430, D- 69120 Heidelberg, Germany. E-mail: franz.schaefer@med.uni-heidelberg.de*

[2]See Appendix for list of investigators.

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children receiving chronic peritoneal dialysis (PD) around the globe. It is hoped that this internet-based registry will overcome the problem of small numbers in pediatric ESRD research and provide the critical mass necessary to identify risk factors and surrogate markers for various clinical outcomes, test the validity of current clinical practice guidelines and provide a database for the development of new guidelines. In this study, we provide an in-depth analysis of the clinical features, determinants and treatment of CKD–MBD, assess compliance with international pediatric CKD–MBD guidelines and attempt to define a rational PTH target range for children receiving chronic PD.

RESULTS

Signs and symptoms of CKD–MBD

Clinical symptoms and/or radiological signs of bone disease were observed in 139 of the 890 patients at registry entry (15%). These included (more than one item per patient permitted) radiological signs of osteodystrophy/rickets (9.4%), radiological osteopenia (4.5%), limb deformities (5%) and current bone pain (1.4%). Eight additional patients (0.9%) had syndromal osteodysplasias. Tissue calcifications were reported in 14 patients (1.5%). Serum biochemistry according to signs and symptoms of bone disease is given in Table 1.

Among 271 patients followed for 12 months, signs and symptoms of CKD–MBD persisted in 20 (7.4%), resolved in 32 (11.8%) and developed *de novo* in 17 (6.3%). Their biochemical and treatment characteristics are given in Table 2.

Biochemical profile

Biochemistry statistics for the total population are given in Table 1. Mean serum PTH was slightly higher in girls ($n = 401$; median 277, interquartile range 144–550 pg/ml) than in boys ($n = 489$; 246, 121–486 pg/ml, $P = 0.05$), whereas serum Ca and Pi levels did not differ between sexes. Serum Pi was higher in 171 post-pubertal (1.85 ± 0.47 mmol/l) than in 719 pre- and early pubertal patients (1.72 ± 0.40 mmol/l, $P < 0.0005$).

The 447 oligoanuric patients (daily urine output < 300 ml/m^2) had significantly higher serum Ca (2.40 ± 0.24 versus 2.35 ± 0.23 mmol/l, $P < 0.01$) and serum Pi (1.79 ± 0.42 versus 1.69 ± 0.37 mmol/l, $P < 0.0001$) than patients with greater residual diuresis, whereas urine output did not affect serum PTH.

The biochemical profile is stratified by PD modality in Table 3. Mean serum Ca was lower with continuous ambulatory PD than on automated PD; this was associated with significantly lower dialysate Ca exposure resulting from lower daily PD fluid turnover and a lower proportion of solutions with supraphysiological dialysate Ca content.

A univariate correlation matrix of factors associated with mean serum PTH and mineral electrolytes is given in Table 4. By categorical analysis, patients with time-averaged PTH < 100 pg/ml showed a 23.8% prevalence of hypercalcemia (mean serum Ca > 2.7 mmol/l at age < 1 year, > 2.57 mmol/l at 1–6 years and > 2.55 mmol/l at age > 6 years[1]), as compared with 10–15% in patients with mean PTH ranging 100–200, 200–300, 300–500 and > 500 pg/ml ($P < 0.0001$).

Table 1 | Serum biochemistry in pediatric patients with clinical and/or radiological signs of CKD–MBD at first observation

	N	PTH (pg/ml)	Ca (mmol/l)	Pi (mmol/l)
All patients	890	257 (126–523)	2.37 ± 0.24	1.75 ± 0.41
Bone pain				
Yes	13	488 (423–1495)****	2.39 ± 0.15	2.1 ± 0.47***
No	877	255 (121–520)	2.37 ± 0.24	1.74 ± 0.47
Bone deformities				
Yes	45	378 (178–1020)**	2.39 ± 0.22	1.79 ± 0.45
No	845	243 (124–510)	2.37 ± 0.24	1.74 ± 0.41
Tissue calcification				
Yes	14	248 (160–582)	2.50 ± 0.30	2.11 ± 0.7*
No	876	257 (125–523)	2.48 ± 0.24	1.75 ± 0.5
Radiological osteodystrophy				
Yes	84	492 (214–964)****	2.38 ± 0.34	1.93 ± 0.5***
No	806	245 (120–455)	2.37 ± 0.23	1.73 ± 0.40
Radiological osteopenia				
Yes	40	275 (158–529)*	2.46 ± 0.23*	1.86 ± 0.4*
No	850	256 (125–519)	2.37 ± 0.24	1.75 ± 0.5

Abbreviations: CKD, chronic kidney disease; MBD, mineral and bone disorder; Pi, inorganic phosphorus; PTH, parathyroid hormone.
Data are median (interquartile range) for PTH, mean ± s.d. for other parameters.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0005$.

Stepwise multiple linear and logistic regression analyses were performed to identify the independent predictors of PTH, Ca and Pi, factoring in age, gender, dialysis vintage, biochemical variables, residual renal function, dialysis modalities and exposure to the medications. Log-transformed mean PTH concentrations were independently predicted by mean serum Ca (regression coefficient ß: −0.772, partial R^2: 0.03, $P < 0.0001$), serum Pi (ß: 0.348, partial R^2: 0.019, $P < 0.0001$), serum bicarbonate (ß: −0.026, partial R^2: 0.007, $P = 0.009$), time on dialysis (ß: 0.035, partial R^2: 0.012, $P = 0.01$) and female sex (ß: 0.18, partial R^2: 0.008, $P = 0.008$).

The risk of a having a mean serum PTH concentration > 300 pg/ml was independently increased by higher serum Pi (for unit 0.1 mmol/l: odds ratio (OR) 1.06, 95% confidence interval (CI) 1.02–1.1, $P < 0.01$) and longer duration of dialysis (for unit years: OR 1.11, CI 1.00–1.20, $P < 0.05$), and reduced by higher mean serum Ca (for unit 0.1 mmol/l: OR 0.83, CI 0.83–0.95, $P < 0.01$), the use of supraphysiological dialysate Ca concentrations (OR 0.55, CI 0.40–0.76, $P < 0.0005$) and higher serum bicarbonate levels (for unit mmol/l: OR 0.94, CI 0.90–0.99, $P < 0.02$).

Mean serum Ca concentrations were predicted by dialysate Ca exposure (ß: 0.06, partial R^2: 0.024, $P < 0.0001$), patient age (ß: −0.047, partial R^2: 0.017, $P = 0.0005$), and serum bicarbonate (ß: 0.055, partial R^2: 0.007, $P = 0.02$). Mean serum Pi levels were affected by residual diuresis (ß: −0.867, partial R^2: 0.023, $P < 0.0001$) and pubertal status (ß: 0.292, partial R^2: 0.008, $P < 0.01$).

Figure 1 depicts the percentage of mean laboratory values of Ca, P and PTH within, below and above the range

Table 2 | Biochemical and treatment characteristics of 271 patients followed prospectively for 12 months, in whom CKD–MBD signs and symptoms persisted, developed *de novo*, resolved or remained absent

	Persistent	*De novo*	Resolved	Absent
N	20	17	32	202
Serum PTH (pg/ml)	411 (290–591)^{ab}	577 (290–733)^{a}	275 (162–488)^{b}	269 (159–443)^{b}
Serum Ca (mmol/l)	2.46 ± 0.24	2.36 ± 0.24	2.39 ± 0.16	2.40 ± 0.17
Serum Pi (mmol/l)	1.73 ± 0.38	1.68 ± 0.49	1.78 ± 0.36	1.72 ± .28
% Time on vitamin D	58 ± 45^{a}	20 ± 36^{b}	33 ± 41^{b}	25 ± 35^{b}
% Time on active vitamin D analogue	90 ± 19	87 ± 20	89 ± 20	74 ± 31
% Time on Ca-containing phosphate binder	59 ± 45^{a}	52 ± 44^{a}	85 ± 28^{b}	86 ± 30^{b}
% Time on Ca-free phosphate binder	28 ± 45^{ab}	41 ± 51^{a}	32 ± 41^{ab}	13 ± 27^{ab}
% Time on cinacalcet	0^{a}	7.3 ± 1.8^{b}	3.1 ± 1.3^{ab}	0.9 ± 0.7^{a}

Abbreviations: CKD, chronic kidney disease; MBD, mineral and bone disorder; Pi, inorganic phosphorus; PTH, parathyroid hormone.
Drug treatment is given as the fractional observation time spent on treatment. Numbers are mean ± s.d. for normally distributed, and median (interquartile range) for skewed parameters. Different superscript letters within a row denote significant differences between groups.

Table 3 | Dialytic calcium exposure and mineral metabolism by PD modality

	CAPD	NIPD	CCPD
N	232	318	320
Residual urine volume (ml per m^2 per day)	670 (100–1250)^{a}	640 (100–1100)^{a}	140 (0–540)^{b}
Daily PD fluid turnover (l per m^2 per day)	4.47 ± 1.95^{a}	7.53 ± 6.90^{b}	8.27 ± 6.78^{b}
Dialysate calcium (mmol/l)	1.32 ± 0.18^{a}	1.36 ± 0.22^{a}	1.43 ± 0.25^{b}
Dialysate calcium exposure (mmol per m^2 per day)	6.12 ± 3.24^{a}	9.30 ± 4.86^{b}	11.0 ± 4.54^{c}
Serum PTH (pg/ml)	256 (128–538)	272 (135–575)	259 (125–492)
Serum Ca (mmol/l)	2.34 ± 0.21^{a}	2.38 ± 0.25^{b}	2.39 ± 0.26^{b}
Serum Pi (mmol/l)	1.71 ± 0.39	1.73 ± 0.38	1.78 ± 0.45

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; NIPD, nocturnal intermittent peritoneal dialysis; PD, peritoneal dialysis; Pi, inorganic phosphorus; PTH, parathyroid hormone.
Numbers are mean ± s.d. for normally distributed, and median (interquartile range) for skewed parameters. Different superscript letters within a row denote significant differences between groups. Twenty patients with 'other' PD modality were excluded from this analysis.

Table 4 | Factors correlated with PTH and mineral electrolyte profile

	PTH	Ca	Pi
Age		−0.10**	0.08*
PD duration	0.17****		
Serum Ca	−0.19****		
Serum Pi	0.13***		
Serum bicarbonate	−0.11***	0.18****	−0.09**
Mean urine volume		−0.09**	−0.15****
Dialysate Ca exposure		0.15****	0.10***
Urinary creatinine clearance			−0.22****
Dialytic creatinine clearance		−0.13**	0.11*
Total creatinine clearance		−0.17***	−0.17***
Active vitamin D analogue	0.30****		
Oral calcium (suppl./binders)		−0.10**	

Abbreviations: PD, peritoneal dialysis; Pi, inorganic phosphorus; PTH, parathyroid hormone; suppl., supplements.
Values are Spearman's correlation coefficients, asterisks indicate significance level (****$P<0.0001$, ***$P<0.001$, **$P<0.01$, *$P<0.05$). Intra-patient mean values were calculated from all available data points in this mixed longitudinal study. For medications, fractional time of drug exposure (never=0, throughout observation=1) was used for correlation analysis. Data pairs were available from 890 patients for all parameters except residual and dialytic creatinine clearance (available in 411 patients).

recommended in the Kidney Disease Outcomes Quality Initiative (KDOQI) and PTH values according to Kidney Disease: Improvement of Global Outcome (KDIGO) guidelines for the different pediatric age groups. The proportion of patients with elevated serum Pi was higher in adolescents (Pi: $P<0.0001$).

Pharmacological treatment of CKD–MBD

The distribution of medications administered to control mineral metabolism and HPT is listed by age group in Table 5. Treatment with calcium-free and calcium-containing phosphate binders, 25OH-vitamin D_3 and active vitamin D analogs did not affect serum Ca and Pi levels. However, mean PTH levels were significantly higher in patients receiving active vitamin D analogs (median 325, interquartile range 155–598 pg/ml) than in untreated patients (median 167, interquartile range 94–301 pg/ml, $P<0.0001$). Of the 356 patients with mean PTH levels below 200 pg/ml, 127 (36%) received no active vitamin D analogs throughout follow-up.

Prediction of CKD–MBD by PTH

The data available in this study was used to identify the range of PTH associated with the lowest likelihood of complications of CKD–MBD. These were defined (a) in the total cohort by the presence of radiological signs of uremic osteodystrophy and/or osteopenia, bone pain, limb deformities or extraosseous calcifications at any time during the observation period, and (b) in the 271 patients followed prospectively for 12 months by the persistence or *de novo* development of signs and symptoms of CKD–MBD.

The rate of patients with CKD–MBD complications at any time was significantly increased when mean PTH levels exceeded 300 pg/ml (Figure 2). Various PTH target ranges were tested by receiver operating characteristic analysis with

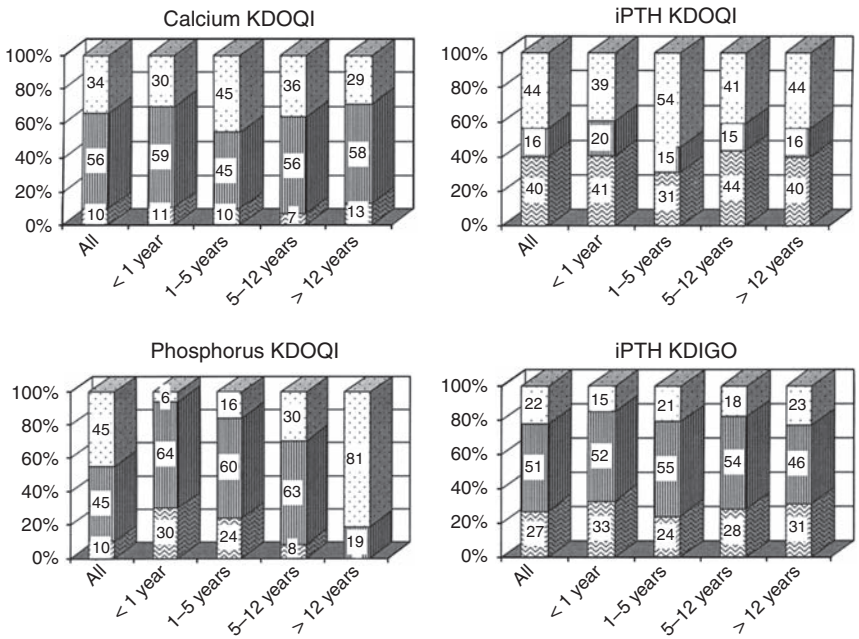

Figure 1 | Fractional distribution of patients with mean serum Ca, inorganic phosphorus, intact parathyroid hormone (iPTH) within (vertical lines), below (undulating lines) and above (dotted) target values as recommended by Kidney Disease Outcomes Quality Initiative (KDOQI), and mean serum PTH as recommended by Kidney Disease: Improvement of Global Outcome (KDIGO) Guidelines.

systematic variation of upper and lower cutoff values of mean PTH. The optimal PTH target range was 10–300 pg/ml (area 0.625 ± 0.019), which predicted the absence of CKD–MBD complications with 60.4% sensitivity and 64.6% specificity. The 200–300 pg/ml target recommended by KDOQI (0.527 ± 0.013, $P < 0.0001$) and the two- to threefold upper limit of normal target suggested by the European Pediatric Dialysis Working Group (EPDWG) (area 0.536 ± 0.012, $P < 0.0001$) were of inferior predictive value, as they excluded many asymptomatic patients, resulting in greater reduction in sensitivity (16.5 and 15.2%) than gain in specificity (88.9 and 91.9%). The KDIGO target range of two- to ninefold the upper normal limit also showed inferior predictive performance (area 0.575 ± 0.012, $P < 0.05$), mainly because of the lower specificity (48.4%) as it encompassed many patients with active CKD–MBD.

Likewise, in the longitudinal analysis the resolution or persistent absence of CKD–MBD signs and symptoms was better predicted by time-averaged PTH between 10 and 300 pg/ml (area 0.632 ± 0.041, sensitivity 53.4%, specificity 73%) than by the KDOQI (area 0.506 ± 0.033, $P < 0.0001$, sensitivity 17.5%, specificity 83.8%) and EPDWG target ranges (area 0.564 ± 0.011, $P = 0.08$, sensitivity 12.8%, specificity 100%), whereas the KDIGO target range was of equivalent overall predictive usefulness (area 0.610 ± 0.044, non-significant) as a result of higher sensitivity (67.9%) and lower specificity (54.1%).

Regional variation of CKD–MBD

Clinical or radiological bone disease showed significant regional variation ($P < 0.0001$), being reported most frequently in North America (39%) and least commonly in Asia (7.5%). The biochemical profiles and medications according to regions are given in Table 6, and median time-integrated PTH levels by country in Figure 3. PTH levels were highest in Latin American countries and in the United States and lowest in European children, with reciprocal differences in serum Ca. The PTH variation among regions remained highly significant ($P < 0.0001$) even when controlling for patient age and sex, PD duration and serum Ca, Pi and bicarbonate levels. Serum Pi levels were highest in North American and lowest in Latin American patients. The significant regional variation of serum Pi persisted when correcting for residual diuresis and pubertal status, PD modality and the use of phosphate binders ($P < 0.001$).

CKD–MBD and longitudinal growth

The analysis of statural growth was restricted to 214 pre- and early pubertal patients (Tanner stages 1–3) with at least 12 months of longitudinal follow-up. Mean height standard deviation score (SDS) at first observation was -2.43 ± 1.64; height was below the third percentile in 39% of children. The annual prospective change in height SDS (mean: -0.03 ± 1.1 per year) tended to be inversely correlated with the mean plasma PTH levels ($r = -0.11$, $P = 0.08$) (Figure 4). Patients with mean PTH >500 ng/ml exhibited a significant loss in height SDS (-0.28 ± 0.52 SDS per year) as compared with children with lower PTH levels (-0.05 ± 0.71; $P < 0.05$) The inverse correlation between change in height SDS and mean PTH became more consistent with longer follow-up, and was highly significant in the 93 children observed for at least 18 months ($r = -0,28$, $P = 0.005$).

Table 5 | Pharmacological treatment of CKD–MBD in pediatric CPD patients stratified by age

	<1 year	1–5 years	6–11 years	>12 years	All
N	67	184	291	348	890
Phosphate binders (any)	61.2%	82.7%	89.7%	95.7%	88.3%
Calcium carbonate/acetate	53.7%	71.7%	71.5%	67.8%	68.8%
Sevelamer	4.5%	2.7%	7.2%	10.6%	7.4%
Calcium carbonate acetate+sevelamer	3%	8.2%	11%	16.4%	11.8%
Lanthanum carbonate	0%	0%	0%	0.8%	0.3%
25-OH-vitamin D_3	29.8%	30.2%	22.3%	23.3%	24.9%
Active vitamin D analogue (any)	58.2%	81.4%	71.5%	76.4%	74.5%
Calcitriol	26.9%	48.9%	47.1%	51.9%	47.8%
1α-calcidiol	31.3%	31.9%	22.7%	22.8%	25.3%
Paricalcitol	0%	0.6%	1%	1.7%	1.1%
Doxercalciferol	0%	0%	0.7%	0%	0.2%
Cinacalcet	0%	0%	1.4%	6.1%	2.8%

Abbreviations: CPD, chronic peritoneal dialysis; CKD, chronic kidney disease; MBD, mineral and bone disorder.

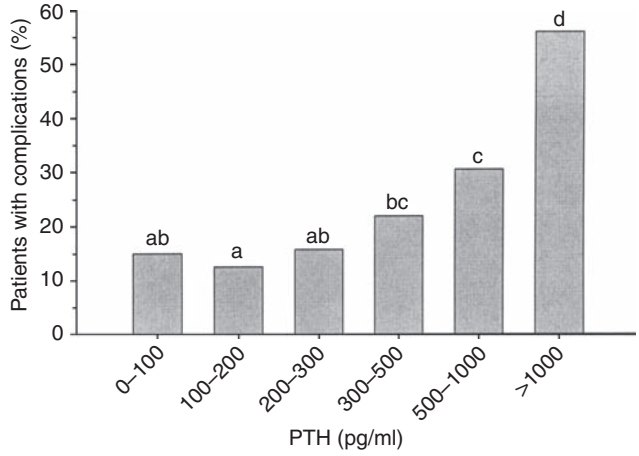

Figure 2 | Percentage of patients with alterations of bone and mineral metabolism (bone pain, limb deformities, extraosseous calcifications, radiological osteomalacia and/or osteopenia) stratified by time-averaged mean parathyroid hormone (PTH) levels. Groups sharing same letters do not differ significantly.

In a logistic regression analysis, the likelihood of catch-up growth (defined by a positive change in height SDS) independently increased with growth hormone therapy (OR 7.21; CI 2.53–20.6, $P=0.0002$), preserved residual diuresis >300 ml per m^2 per day (OR 3.25; CI 1.66–6.31, $P=0.0006$) and patient age (OR 1.07; CI 1.1.0–1.14, $P=0.04$), and decreased with higher baseline height SDS (OR 0.72; CI 0.59–0.88, $P=0.001$) and, with borderline significance, with higher mean PTH levels (OR for unit 100 pg/ml: 0.90; CI 0.80–1.01, $P=0.07$). The likelihood of catch-up growth was independent of gender or duration of ESRD.

An analysis of covariance was performed to further explore a potential interaction of PTH levels with growth hormone therapy. Whereas, patients receiving growth hormone generally showed more positive height SDS changes than untreated patients, the slopes of the association of PTH with change in height SDS did not differ significantly between children with and without growth hormone therapy ($P=0.88$), indicating that growth hormone promoted growth independent of the prevailing serum PTH level.

DISCUSSION

This study demonstrates that CKD–MBD remains a significant problem in children on chronic dialysis. On a global scale, at least one in six children shows radiological and/or clinical signs of bone disease and 44% exhibit severe secondary HPT with PTH levels exceeding five times the upper limit of normal. At the other end of the bone disease spectrum, 4.5% of patients showed isolated radiological osteopenia with higher serum calcium and lower PTH levels, compatible with a state of low bone turnover. All these conditions were associated with an elevated serum Ca×Pi product, compatible with the notion that both types of uremic bone-mineral disorder may increase the risk of extraosseous calcification.[4]

The analysis of the mineral biochemistry profiles revealed several interesting associations. Higher serum calcium levels were independently associated with younger patient age, probably reflecting the higher physiological range of serum calcium in infants. Dialytic Ca exposure was an additional independent positive predictor of serum Ca. Continuous

Table 6 | Regional variation of mineral metabolism

	Latin America	North America	Europe	Turkey	Asia
N	201	129	324	142	94
Serum Ca (mmol/l)	2.33 ± 0.24^{a}	2.39 ± 0.30^{ab}	2.41 ± 0.23^{b}	2.33 ± 0.21^{a}	2.37 ± 0.19^{ab}
Serum Pi (mmol/l)	1.66 ± 0.35^{a}	1.91 ± 0.55^{b}	1.71 ± 0.36^{ac}	1.79 ± 0.41^{c}	1.77 ± 0.43^{ac}
Serum PTH (pg/ml)	418 (245–733)^{a}	290 (163–627)^{a}	175 (87–377)^{b}	297 (152–548)^{a}	208 (121–331)^{b}
PD fluid Ca^{2+} concentration	1.27 ± 0.12^{a}	1.49 ± 0.28^{b}	1.41 ± 0.23^{c}	1.31 ± 0.16^{a}	1.42 ± 0.27^{c}
Dialysis modalities (%) CAPD/APD/CCPD/other	32/51/16/1	4/16/79/1	13/46/39/2	60/20/19/1	38/19/33/10
Ca-containing phosphate binders	91.4%^{a}	57.8%^{b}	76.9%^{c}	87.0%^{a}	89.4%^{a}
Ca-free phosphate binders	3.1%^{a}	45.5%^{b}	28.1%^{c}	7.1%^{a}	32.2%^{c}
25-OH-vitamin D_3	26.0%^{ab}	18.6%^{bc}	35.6%^{a}	10.2%^{c}	32.8%^{a}
Active vitamin D analogues	72.0%^{ab}	74.8%^{ab}	81.6%^{a}	66.6%^{b}	67.3%^{b}
Cinacalcet	0.5%^{a}	9.6%^{b}	2.4%^{a}	0.7%^{a}	2.0%^{a}

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; Pi, inorganic phosphorus; PTH, parathyroid hormone.
Numbers are median (interquartile range) for PTH and mean ± s.d. for other parameters. Different superscript letters within a row denote significant differences between groups ($P<0.05$).

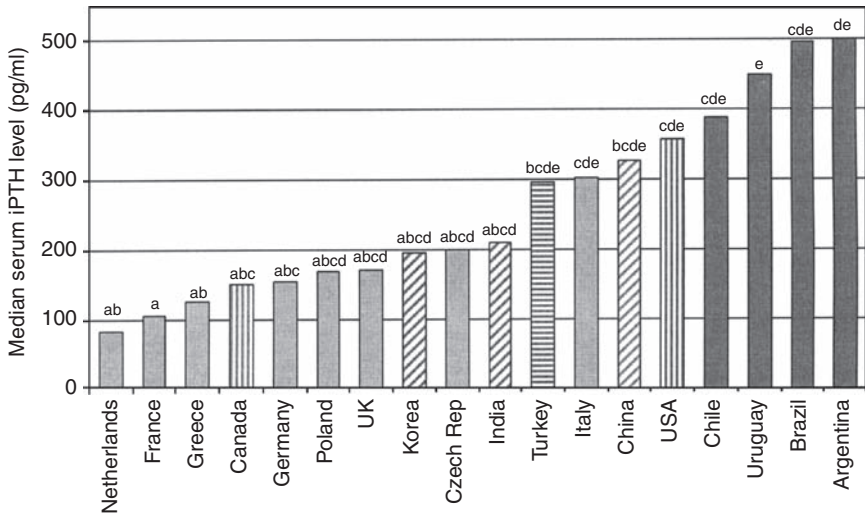

Figure 3 | Variation of intact parathyroid hormone (iPTH) control by country. Only countries with ⩾15 registered patients were considered. Bars denote medians of patient-specific time-averaged mean PTH levels. European countries light gray, Latin American countries dark grey, Turkey horizontally dashed, North America vertically dashed, Asian countries diagonally dashed bars. Letters denote significances ($P<0.05$) in Student Newman–Keuls multiple comparison testing of log-transformed means; countries sharing same letters do not differ significantly.

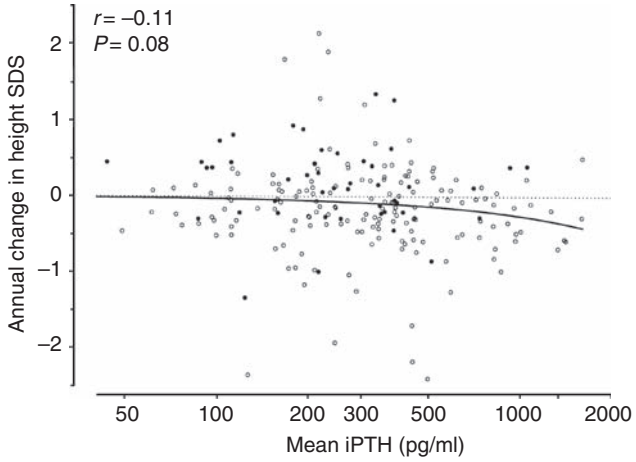

Figure 4 | Time-averaged mean plasma intact parathyroid hormone (iPTH) concentrations and change in standardized height in 214 pre- and early pubertal children followed prospectively for at least 12 months. Full circles indicate patients receiving recombinant growth hormone. SDS, standard deviation score.

cycling PD patients were exposed to higher amounts of PD fluid with a higher average Ca concentration than children undergoing continuous ambulatory PD, resulting in a considerably higher dialysate-plasma Ca^{2+} gradient and, consequently, higher serum Ca levels. Surprisingly, the use of calcium containing phosphate binders and active vitamin D analogs was not predictive of serum Ca. We speculate that the avoidance of these drugs in patients prone to hypercalcemia and their preferential administration in hypocalcemic patients concealed their calcemic properties in the cohort analysis.

Mean serum Ca and Pi were significantly higher in oligoanuric patients. Residual urine volume was the strongest independent predictor of the risk of developing an elevated Ca⋆Pi product, indicating a crucial role of residual renal function for mineral electrolyte homeostasis in children receiving chronic PD.

Hyperphosphatemia was more common in adolescents despite higher phosphate binder prescription, likely reflecting poor medication adherence during puberty, a period of changing food preferences and increased psychological and social stress leading to rejection of disease-related restrictions.

Of particular interest in this global study is the significant regional variation in mineral metabolism control. Serum Pi levels were highest in North American and lowest in Latin American patients. As these differences were independent of residual renal function, pubertal status, PD modality and phosphate binder prescription, regional diversity in nutritional phosphorus intake related to cultural preferences and patient adherence with nutritional advice may be the most likely explanation of the observed differences.

The main determinants of plasma PTH were serum Ca, Pi and bicarbonate levels as well as dialysis vintage. The risk of mean PTH exceeding 300 pg/ml increased by 12% per 0.1 mmol/l decrease in Ca, by 5% per 0.1 mmol/l increase in Pi and by 5% per 0.1 mmol/l decrease in bicarbonate. These findings re-emphasize the importance of serum Ca in PTH control. Even low normal Ca, as recommended in the pediatric KDOQI guidelines, may increase the risk of developing severe HPT. The use of Ca-containing phosphate binders was not correlated with mean PTH levels and the administration of active vitamin D analogs even showed a positive relationship, reflecting physicians' responses to patients' therapeutic demands. Notably, the calcium content of the PD fluid, probably the most steady determinant of calcium balance in chronic PD patients, was an independent negative predictor of PTH, suggesting effective modulation of PTH levels by fluid calcium content.

The consistent inverse relationship of PTH with serum bicarbonate levels is in keeping with observational and preliminary interventional study evidence in adult patients supporting a direct stimulatory effect of acidosis on PTH secretion.[5–7] It has been proposed that acidosis may reduce the sensitivity of the Ca sensing receptor to circulating Ca by inducing conformational alterations in the Ca-binding sites.[8]

Female gender was another cofactor predisposing to more marked HPT. This observation is in line with the threefold higher prevalence of primary HPT in women,[9] the reduced PTH suppressibility and faster progression to parathyroid nodular hyperplasia in female hemodialysis patients, and the diminished antiproliferative efficacy of calcitriol on explanted female parathyroid tissue.[10–12] Although this gender difference has been related to a direct stimulatory action of estrogen on the parathyroid,[13] we observed higher PTH levels across all age groups independent of pubertal status consistent with an intrinsic gender dimorphism in parathyroid function.

In addition to and independent of all these factors, severe HPT occurred with a 10% higher likelihood with each year on dialysis, compatible with gradual development of parathyroid gland autonomy over time.

Two specific pediatric CKD–MBD guidelines have been released, one by KDOQI and the other by the EPDWG.[1,2] Recently, KDIGO released CKD–MBD recommendations applicable to both adults and children.[3] These guidelines markedly differ with respect to the recommended PTH target range: whereas the KDOQI document recommended to maintain concentrations at 200–300 pg/ml, the EPDWG proposed two to three times the upper limit of the normal range (that is, approximately 120–180 pg/ml) and the recent KDIGO guideline defines a range between two and nine times the upper limit of normal (that is, approximately 120–500 pg/ml) as acceptable. This survey demonstrates that adherence to the PTH guideline targets remains an elusive goal, with 59% of children exceeding the upper limit of the EPDWG, 44% that of the KDOQI, and 20% that of the KDIGO target range. In addition, a sizable fraction exhibited PTH levels below the lower end of the target ranges, resulting in <1 in six patients maintaining PTH within the KDOQI target. The comparison of PTH levels by country disclosed remarkable regional differences, with three- to fivefold higher mean levels in the Latin American countries and the United States as compared with most of the European countries. The PTH variation mirrored in part reciprocal differences in serum Ca but remained highly significant after correction for Ca, and persisted when additionally accounting for Pi and bicarbonate levels, age, gender and dialysis vintage. Hence, the regional differences in PTH control might primarily reflect divergent therapeutic policies. Indeed, the median PTH level in the European centers matched the European guidelines, whereas the PTH median value in the North American centers was well within the target range of the KDOQI guidelines. The prescription of vitamin D and active vitamin D analogs was highest in the European centers, possibly reflecting a lower threshold of using these drugs to suppress PTH to the lower target range preferred in Europe.

The optimal PTH target for children is a matter of long-standing controversy. Bone histopathology studies, considered gold standard in assessing CKD–MBD, have been performed in limited numbers of pediatric patients with partially conflicting results.[14–17] Whereas markedly elevated PTH levels are associated with osteitis fibrosa, a possible correlation of normal or mildly elevated PTH with low turnover bone disease appears less clear.

The detailed clinical information collected in the registry allowed us to address the relationship of serum PTH with signs and symptoms of bone disease. The prevalence, persistence and *de novo* development of clinical and/or radiological CKD–MBD were clearly associated with exposure to PTH levels exceeding 300 pg/ml. A receiver operating characteristic analysis comparing the power of different PTH ranges to predict the absence of CKD–MBD related morbidity supported an acceptable limit of 10–300 pg/ml. This range includes symptom-free patients with superior sensitivity than the narrower KDOQI and EPDWG targets, and better specificity than the KDIGO target range, which tends to include a sizable fraction of symptomatic patients with PTH between 300–500 pg/ml.

Longitudinal growth, a treatment end point peculiar to the pediatric population, is a potential indirect surrogate marker of bone health. Weak positive correlations between PTH levels and growth rates were found in some but not confirmed by other studies of children with CKD and on dialysis.[18–22] In addition, growth rates did not differ between children with low bone turnover and other histomorphometric phenotypes.[17] Overcoming the size limitations and potential selection bias of previous studies, our longitudinal analysis of >200 pre- and early pubertal children disclosed a slight negative association of relative growth with PTH exceeding 500 pg/ml, which was independent of residual renal function and growth hormone therapy, the main covariates of statural growth in this population. Our analysis provides factual evidence that low PTH levels are not associated with impaired statural growth.

Although the analysis of clinical and radiological bone disease and statural growth provides an idea about the acceptable upper limit of the PTH target range in children, serum calcium levels over time were available as a surrogate marker of potential low bone turnover. The fraction of patients with consistent hypercalcemia increased with PTH levels below 100 pg/ml, providing a rationale to use this level as a lower target limit. In this context, it is worth mentioning that many children on chronic PD retain PTH concentrations between 100 and 200 pg/ml without hypercalcemia or osteopenia and with good longitudinal growth. More than a third of the children with mean PTH <200 pg/ml did not receive any active vitamin D analogue treatment.

In conclusion, this analysis of a global pediatric ESRD cohort highlights the wide variability of CKD–MBD and identifies residual renal function, dialysis vintage, gender, pubertal status,

serum bicarbonate and dialysate calcium content as important determinants of mineral metabolism and PTH control. We observed major regional variation in the manifestations and management of pediatric CKD–MBD. Although morbidity from CKD–MBD clearly increased with PTH levels >300 pg/ml, the PTH–calcium relationship indicates 100 pg/ml as a reasonable lower target limit. We recognize the limitations of this registry-based analysis, which lacks sensitive information on bone and vascular morphology and function and conclusive long-term end points, such as late fracture and cardiovascular event rates. It is hoped that the IPPN will contribute to the generation of such prospective information as it continues to follow children with ESRD around the globe.

MATERIALS AND METHODS

Data collection

The IPPN registry collects information from children and adolescents treated with chronic PD in 75 pediatric dialysis centers in 27 countries around the globe. All prevalent and incident consenting patients in each participating center are enrolled and followed until discontinuation of PD. Because of the voluntary character of the registry, the nationwide coverage of pediatric PD patients varies between countries (for example, US 11%; Turkey 19%; 12 European countries 31%; Canada 59%; Chile, Korea, Argentina, Singapore, Nicaragua: 80–100%). Data input to the IPPN registry is performed exclusively via an Internet-based web platform (http://www.pedpd.org). Data pertaining to basic patient and PD modality characteristics, growth and weight gain, serum biochemistry results, complications associated with the uremic state and dialysis, PD-related and other infections, hospitalizations, and information about pharmacological treatment are submitted every 6 months. The data is automatically checked for accuracy and completeness. In addition, center-specific demographic data and PD practices are collected at the time of center registration. Data protection is ensured by pseudonymized data input.

The registry protocol was approved by the ethical committees/institutional review boards as required at each participating center. Written parental consent and, whenever appropriate, assent from patients is obtained.

Patients

Between April 2007 and June 2009, data on 890 prevalent pediatric patients receiving chronic PD followed in 61 centers in 24 countries in Europe, the Americas and Asia were reported to the IPPN registry (see Appendix). Patients were aged 1 month to 19.9 (median 10.3) years at time of enrollment. The underlying kidney disorders included renal hypodyspasia with or without obstructive or refluxive uropathy (42.3%), steroid-resistant nephrotic syndrome (19.1%), other glomerulopathies (8.3%), hemolytic uremic syndrome (6.2%), nephronophthisis (5.4%), polycystic kidney disease (4.9%), systemic vasculitis (3.8%), post-ischemic renal disease (2.5%), metabolic disease (2.3%) and others/unknown (5.2%).

Mean duration of ESRD at the time of enrollment was 2.4 ± 2.5 years and PD vintage 1.9 ± 1.7 (0.1–11.8) years. In all, 11% of patients were enrolled within 3 months of PD initiation. At 6-, 12-, 18-, and 24-month follow-ups, data were available in 530, 270, 117 and 40 of the 890 patients, respectively. PD solutions with neutral calcium content (1.25–1.35 mmol/l) were used in 65%, high calcium (1.75 mmol/l) in 30% and low calcium (<1.25 mmol/l) in 5% of patients.

PTH assays

Second generation PTH assays were used in 58 of 61 centers. These included direct chemiluminescence assays (DPC Biermann/SIEMENS Medical Solutions Diagnostics, Bad Nauheim, Germany, Beckman Access, Beckman Coulter, Brea, CA, USA, Diasorin Liaison N-tact PTH, Diasorin, Saluggia, Italy) in 43.3%, the Roche (Hoffmann-La Roche, Basel, Switzerland) Elecsys iPTH electrochemiluminescence assay in 27.2%, immunoradiometric assays (CIS-Bio ELSA PTH, CIS-bio, Berlin, Germany, Biosource Europe iPTH-120min-IRMA, DIAsource ImmunoAssays, Nivelles, Belgium) in 21.9% and ELISAs (Biomerica ELISA iPTH, Biomerica, Irvine, CA, USA, Tosoh Intact PTH, Tosoh Bioscience, South San Francisco, CA, USA) in 2.4% of measurements. Two centers used the Nichols' Advantage third generation bioIntact PTH assay, and one center the Scantibodies third generation whole-PTH assay). To eliminate assay-related systematic differences in PTH concentrations, the reported PTH values were normalized by applying the assay-specific conversion factors suggested by Souberbielle *et al.*[23,24] Reported PTH concentrations were divided by 0.9 for the Liaison N-tact PTH, by 0.7 for the bioIntact PTH Advantage and by 0.55 for the Scantibodies whole-PTH assay. These conversions applied to 10.1% of all PTH measurements in the study.

Statistics

Time integrated means were calculated for the biochemical parameters according to individual observation times. Height was normalized to SDSs, using the World Health Organization 2006 normative values for children up to age 5 years and the National Center for Health Statistics 2000 reference charts for older children.[25,26] The annualized change in height SDS was calculated in all children with at least 6 months follow-up.

Data was checked for normal distribution by the Kolmogorov–Smirnoff test. Differences in group means (log-transformed in case of non-Gaussian distribution) were assessed by Student's t test for two-group comparisons, and by analysis of variance followed by Student's Newman–Keuls testing for multiple comparisons. Differences in proportions were assessed by χ^2 testing. Stepwise multiple linear regression and logistic regression were used for multivariate data analysis as appropriate. Receiver operating characteristic analysis was performed to identify the PTH target range associated with minimal CKD–MBD manifestations.

All data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

DISCLOSURE

FS is a Consultant for Amgen. BAW is consulting for Amgen, Abbott and Genzyme and received speakers' honoraria from Genentech.

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Appendix

The following Principal Investigators are contributing to the International Pediatric Peritoneal Dialysis Network Registry:

Argentina: E Sojo, Hospital de Pediatria Garrahan, Buenos Aires; PA Coccia, Hospital Italiano de Buenos Aires; A Suarez, Hospital de Niños Sor. Maria Ludovica La Plata; PG Valles, Hospital Pediatrico Humberto Notti, Mendoza, R Salim, Rennius SA Salta. **Belgium:** K van Hoeck, University Hospital Antwerp, Edegem. **Brazil:** V Koch, Instituto da Criança–Hospital das Clinicas FMUSP, Sao Paulo. **Canada**: J Feber, Children's Hospital of Eastern Ontario, Ottawa; DA Geary, Hospital for Sick Children, Toronto; C White, BC Children's Hospital, Vancouver. **Chile**: M Valenzuela, Hospital Guillermo Grant Benavente, Concepcion; J Villagra, Hospital Base, Osorno; F Cano, Hospital Luis Calvo Mackenna,Santiago, MA Contreras, Roberto del Rio Hospital, Santiago; A Vogel, Pontivicia Universidad Catolica de Chile, Santiago; P Zambrano, Hospital Dr Gonzales Cortes, Santiago, P Berrocal Hospital Sotero del Rio, Santiago. **China**: MC Chiu, Department of Pediatric and Adolescent Medicine, Hong Kong, H Xu, Children's Hospital of Fudan University, Shanghai. **Czech Republic**: K Vondrak, University Hospital Motol, Prague. **Finland:** K Rönnholm, Hospital for Children and Adolescents, Helsinki; **France**: B Ranchin, Hôpital Femme Mère Enfant, Lyon; T Ulinski, Armand Trousseau Hospital, Paris; M Fischbach, Children's Dialysis Center, Strasbourg. **Germany**: R Büscher, Children's Hospital Essen; M Kemper, University Medical Center, Hamburg; L Pape, Medical School, Hannover; F Schaefer, D Borzych, Center for Pediatrics and Adolescent Medicine, Heidelberg; U John, Kidney Center for Children and Adolescents, Jena; G Klaus, University Hospital, Marburg; D Haffner, University Children's Hospital, Rostock. **Greece:** F Papachristou, Aristoteles University, Thessaloniki. **India:** A Bagga, All India Institute of Medical Sciences, New Delhi; M Kanitkar, Armed Forces Medical College, Pune. **Italy**: E Verrina, G Gaslini Institute, Genova; A Edefonti, Fondazione Ospedale Maggiore Policlinico, Milano; G Leozappa, Dip. Nefrologia-Urologia, Rome. **Israel**: D Landau, Soroka Medical Center, Beer-Sheva. **Korea**: IS Ha, Dialysis Center for Children and Adolescents, Seoul; KH Paik, Samsung Medical Center, Seoul. **Macedonia**: E Sahpazova, Pediatric Clinic, Skopje. **Netherlands**: JW Groothoff, Academic Medical Center, Amsterdam**. Nicaragua:** Y Silva, Hospital Infantil de Nicaragua, Managua. **Poland**: AM Zurowska, D Borzych, Medical University, Gdansk; D Drozdz, University Children's Hospital, Krakow; M Lipka, Children's Memorial Health Institute, Warsaw; M Sczepanska, Dialysis Division for Children, Zabrze. **Romania**: O Brumariu, St Maria Children's Hospital, Iasi. **Singapore:** HK Yap, Shaw-NKF-NUH Children's Kidney Center. **Spain**: G Ariceta, Hospital de Cruces, Baracaldo. **Turkey**: F Ozaltin, Hacettepe University, Ankara; S Bakkaloglu, Gazi University, Ankara; I Bilge, Department of Pediatric Nephrology, Çapa-Istanbul; E Serdaroglu, Dr Behcet Children Research and

Educational Hospital, Izmir; A Bal, Tepecik Children and Research Hospital, Izmir; S Mir, Ege University Faculty of Medicine, Izmir-Bornova. **United Kingdom**: L Rees, Great Ormond Street Hospital, London. AR Watson, Children and Young People's Kidney Unit, Notthingham. **Uruguay**: J Grünberg, SE.N.NI.AD, Montevideo. **USA**: L Greenbaum, Children's Healthcare Pediatric Dialysis Unit, Atlanta; A Neu, Johns Hopkins Hospital, Baltimore; D Askenazi, Children's Hospital of Alabama, Birmingham; D Gipson, University of North Carolina, Chapel Hill; H Patel, Cildren's Hospital, Columbus; S Pottoore, Children's Medical Center, Dallas; V Dharnidharka, Division of Pediatric Nephrology, Gainesville; T Bunchman, Helen DeVos Children's Hospital, Grand Rapids; A Chua, Texas Children's Hospital, Houston; BA Warady, Children's Mercy Hospital, Kansas City; J Zaritsky, UCLA Medical Center, Los Angeles.