Response of different PTH assays to therapy with sevelamer or CaCO₃ and active vitamin D sterols

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Abstract Amino-terminally truncated parathyroid hormone (PTH) fragments are detected to differing degrees by first- and second-generation immunometric PTH assays (PTH-IMAs), and acute changes in serum calcium affect the proportion of these fragments in circulation. However, the effect of chronic calcium changes and different vitamin D doses on these PTH measurements remains to be defined. In this study, 60 pediatric dialysis patients, aged 13.9±0.7 years, with secondary hyperparathyroidism were randomized to 8 months of therapy with oral vitamin D combined with either calcium carbonate (CaCO₃) or sevelamer. Serum phosphorus levels did not differ between groups. Serum calcium levels rose from 9.3±0.1 to 9.7±0.1 mg/dl during CaCO₃ therapy (p<0.01 from baseline) but remained unchanged during sevelamer therapy. In the CaCO₃ and sevelamer groups, baseline serum PTH levels (1st PTH-IMA; Nichols Institute Diagnostics, San Clemente, CA) were 964±75 and 932±89 pg/ml, and levels declined to 491±55 and 543±59 pg/ml, respectively (nonsignificant between groups). Patients treated with sevelamer received higher doses of vitamin D than those treated with CaCO₃. The PTH values obtained by first- and second-generation PTH-IMAs correlated closely throughout therapy and the response of PTH was similar to both PTH-IMAs, despite differences in serum calcium levels.

Keywords Calcium carbonate · Parathyroid hormone · Secondary hyperparathyroidism · Sevelamer · Vitamin D

Introduction

Parathyroid hormone (PTH) levels rise as renal function declines, and these levels are widely used to assess bone turnover and to guide therapy for renal osteodystrophy [1]. Different mid- and C-terminal fragments of the intact PTH molecule accumulate in patients with chronic kidney disease (CKD), complicating the accuracy of the radioimmunoassay PTH measurements in the assessment of parathyroid gland activity [2]. The development of the two-site immunometric assays (IMAs) for the detection of PTH has reduced cross-reactivity with small PTH fragments, yet large amino-terminal truncated PTH fragments (ntPTH) continue to cross-react with first-generation immunometric PTH-IMAs (1st PTH-IMAs) [3–6], thus overestimating the levels of...
biologically active PTH in circulation. At least one of those fragments, PTH(7-84), has been shown to antagonize the calcemic actions of the full-length molecule in vivo [7–9], which may confound the relationship between PTH levels and bone turnover in individuals with CKD. Second-generation immunometric PTH assays (2nd PTH-IMAs) detect exclusively the full-length PTH(1-84) molecule and thus more accurately reflect the concentration of biologically active PTH [10]. While ntPTH cannot be measured selectively by currently available assays, an estimation of their abundance may be obtained by subtracting the value obtained with the 2nd PTH-IMA from the value obtained with the 1st PTH-IMA [11, 12]. This estimate has been postulated by some investigators to have potential clinical significance in the diagnosis of renal osteodystrophy [11, 13], although its utility has not been substantiated by others [12, 14].

Changes in serum calcium, as occur during therapy with calcimimetic agents, have been associated with altered proportions of PTH detected by the 1st and 2nd PTH-IMAs [15], suggesting that therapies which affect serum calcium levels may modify the proportions of PTH(1-84) to ntPTH in circulation. Furthermore, the short-term use of different vitamin D analogues has also been associated with different proportions of PTH(1-84) to ntPTH [16]. In recent years, non-calcium-containing phosphate binders used in conjunction with vitamin D sterols have been shown to control serum phosphate concentrations and the skeletal lesions of secondary hyperparathyroidism as effectively as calcium-based binders, without increasing serum calcium levels [17]. Although PTH levels, as determined by 1st PTH-IMA, have been found to decline to a similar degree regardless of type of phosphate-binding therapy [17], the response of PTH measured by the 2nd PTH-IMA, i.e. excluding the detection of large amino-terminally truncated PTH fragments, to different phosphate binder therapies remains unknown. Thus, our study was designed to evaluate the relative changes in serum PTH levels, as measured by the 1st and 2nd PTH-IMAs, during treatment of secondary hyperparathyroidism with either calcium carbonate (CaCO3) or sevelamer in combination with active vitamin D sterols in pediatric dialysis patients.

Methods

The patients included in this study are part of an ongoing clinical trial designed to evaluate the effects of two vitamin D analogues and two phosphate binders on the control of the skeletal lesions of secondary hyperparathyroidism, as previously reported [17]. Briefly, potential subjects, aged 2–20 years, treated with continuous cycling peritoneal dialysis (CCPD) (2.5 mEq/l calcium dialysate) and with serum PTH levels [1st PTH-IMA; Nichols Institute Diagnostics, San Clemente, CA; hereafter referred to as Nichols] >400 pg/ml were considered as potential candidates for the study. After a 4-week withdrawal period from vitamin D therapy, patients were admitted to the UCLA General Clinical Research Center, and bone biopsies were obtained from the anterior iliac crest using a modified Bordier trephine after double tetracycline labeling; bone quantitative histomorphometry was performed as previously described [18]. Those subjects who had bone histological findings consistent with secondary hyperparathyroidism (i.e. high bone formation rates and/or marrow fibrosis) [19] were randomized into one of four treatment arms for 8 months using a 2×2 study design: group 1, doxercalciferol + CaCO3 (n=16); group 2, doxercalciferol + sevelamer (n=14); group 3, calcitriol + CaCO3 (n=16); group 4, calcitriol + sevelamer (n=14). Exclusion criteria were: history of poor medication compliance, parathyroidectomy within the past 12 months, treatment with prednisone, other immunosuppressive agent(s) or growth hormone within the preceding 6 months, or other bone pathology. During treatment, patients were removed from the study per protocol in the event of either renal transplantation or medication noncompliance, defined as a serum phosphorus level >7 mg/dl for 3 consecutive months. The study was approved by the UCLA Human Subject Protection Committee and informed consent was obtained from all patients and/or parents.

Study protocol

The initial dose of vitamin D was determined by the baseline 1st PTH-IMA (Nichols) concentration, and doses were titrated upwards monthly based on PTH, calcium, and phosphorus values. Patients with 1st PTH-IMA (Nichols) values <600 pg/ml received an initial vitamin D sterol dose of either 0.5 μg (calcitriol) or 2.5 μg (doxercalciferol); those with values >600 pg/ml received 1 μg (calcitriol) or 5 μg (doxercalciferol). All doses were given Monday, Wednesday, and Friday orally at bedtime [17]. The PTH target values were between 300 and 400 pg/ml (1st generation, Nichols), and vitamin D therapy was held for serum calcium values >10.2 mg/dl or serum phosphorus levels >6 mg/dl. Phosphate-binding therapy, in the form of CaCO3 or sevelamer, was titrated to maintain serum phosphorus levels between 4.0 and 6.0 mg/dl [17].

Serum levels of calcium, albumin, and phosphorus were obtained at baseline and biweekly throughout the 8-month course of the study; serum alkaline phosphatase and PTH levels were determined monthly. Biochemical measurements of calcium, albumin, phosphorus, and alkaline phosphatase were determined as previously described [17]. Levels of PTH were determined in plasma by three separate assays: two 1st PTH-IMAs by different manufacturers (Nichols, San Clemente, CA; Immutopics, San Clemente, CA) and one 2nd PTH-IMA (Immutopics). The characteristics of these assays
have been described in earlier reports [10, 12]. Serum calcium levels were corrected for serum albumin levels by the formula: corrected calcium = measured calcium + [0.8 × 4 – (serum albumin)]. While 1st PTH-IMA (Nichols) values were used for vitamin D therapy titration, plasma samples for 1st and 2nd PTH-IMA (Immutopics) were stored at –80°C, and the analyses were performed in batches upon completion of the study period. The ratio of PTH(1-84)/ntPTH was calculated as the measurement of 2nd PTH-IMA (Immutopics)/[1st PTH-IMA (Immutopics) – 2nd PTH-IMA (Immutopics)], as previously described [11, 12, 14].

Statistical analysis

The power of the overall trial was calculated based on a change in bone formation rate from baseline [17]; the biochemical data presented in this study were predetermined secondary endpoints of the study. All data from study subjects were evaluated on an “intent-to-treat” as well as on a “per-protocol” basis. Mean and standard error were used to summarize the outcomes for each treatment group at each time point. Baseline determinations between the two phosphate binder groups were compared using the t test. The results of the descriptive analyses demonstrated a difference in the data from the initial 4-month period to the last 4 months: changes in serum levels of calcium, PTH, and alkaline phosphatase were observed during the first 4 months, while values were stable during the last 4 months of the study. Therefore, the mean values for each treatment group in the last 4 months were estimated, and comparisons between treatment groups were performed. A mixed model, including treatment, time, and treatment by time interactions, was developed to compare differences between the two treatment groups and average changes from baseline within treatment groups. Loess local regression fit lines with 95% confidence intervals (95% CI) were also used to assess differences, as determined by the percentage change from baseline, between different PTH assays. Spearman correlation coefficients were calculated using mixed model coefficients throughout the course of the study. The statistical analyses were performed using SAS software (SAS Institute, Cary, NC), and all tests were two-sided with a significance level of p<0.05.

Results

Study participants

A total of 60 patients (30 males, 30 females) aged 13.9±0.7 years were enrolled in the study. The causes of end-stage kidney disease were equally divided between glomerular disease, obstruction/dysplasia, and unknown etiology. The average time on dialysis was 12±2 months. Eleven subjects had previously undergone renal transplantation; none of these had residual graft function or were on immunosuppressive therapy at the time of the study. Fifty-one patients completed the study, while nine discontinued the study early (five from group 1, two from group 2, one from group 3, and one from group 4) due to renal transplantation (five patients) and medication non-compliance (four patients) as per protocol. As previously described [17], preliminary analysis revealed no interactions between the two vitamin D analogues with respect to any biochemical parameters. Thus, our study was confined to comparisons between the two phosphate binders. No differences in outcomes were observed between intent-to-treat and per-protocol analyses; consequently, only results for the intent-to-treat analysis are described here.

Changes in serum phosphorus, calcium, and alkaline phosphatase levels according to the type of phosphate-binding agent

Baseline serum phosphorus levels were 6.4±0.1 and 6.2±0.2 mg/dl (nonsignificant, NS) in CaCO3- and sevelamer-treated patients, respectively, and the values did not differ between these groups throughout the course of the study (Fig. 1). Initial serum calcium levels were 9.3±0.1 mg/dl in both the CaCO3 and sevelamer groups. Serum levels of calcium rose during the first 4 months and then plateaued in the CaCO3 treatment group; by contrast, values remained unchanged from baseline in the sevelamer group (Fig. 1). Final serum calcium levels were 9.7±0.1 mg/dl (CaCO3) (p<0.01 from baseline) and 9.2±0.2 mg/dl (sevelamer) (NS from baseline, p<0.05 between groups) (Fig. 1). The initial calcium–phosphorus ion products were 51.6±1.6 and 50.7±1.8 in the CaCO3 and sevelamer groups, respectively (NS),
and the final values were 55.1±1.8 and 51.6±1.6 (NS between groups). Forty-eight episodes of hypercalcemia (serum calcium ≥ 10.2 mg/dl) occurred in the CaCO₃ treatment group compared with 17 episodes in the sevelamer group (p<0.01).

Baseline serum alkaline phosphatase levels were 373±38 versus 424±64 IU/l (CaCO₃ vs. sevelamer, NS), and the values declined to 289±42 and 361±57 IU/l in the two groups respectively (p<0.01 from baseline in both groups; NS between groups).

Changes in PTH levels according to the type of phosphate-binding agent

Prior to therapy, PTH values, as determined by the 1st PTH-IMA (Nichols), were 964±75 and 933±89 pg/ml in the CaCO₃ and sevelamer treatment groups, respectively (NS). Irrespective of phosphate binder, PTH values decreased between months 3 through 5 of therapy, reaching a plateau by month 6 (Fig. 2). Average PTH levels during the last 4 months of therapy were 239±44 and 261±32 pg/ml, corresponding to a 54±11% and 47±8% decline (CaCO₃ vs. sevelamer), respectively (p<0.01 from baseline in both groups; NS between groups). The time course of decline in PTH levels as measured by the 2nd PTH-IMA paralleled that of the 1st PTH-IMAs (Fig. 2).

Throughout the course of the study, the PTH values as determined by the different assays were highly correlated: 1st PTH-IMA (Nichols) and 1st PTH-IMA (Immutopics), r=0.81, p<0.01; 1st PTH-IMA (Nichols) and 2nd PTH-IMA (Immutopics), r=0.81, p<0.01; 2nd PTH-IMA (Immutopics) and 1st PTH-IMA (Immutopics), r=0.93, p<0.01.

The ratio of PTH(1-84)/ntPTH did not differ between groups during the course of the study. Average values were 1.9±0.4 and 1.6±0.2 in the CaCO₃ and sevelamer groups, respectively, at the start of the study (NS between groups). Average values during the last 4 months of the study were 1.2±0.1 and 1.5±0.2 in the two groups, respectively (NS between groups; NS from baseline). Despite no differences in the ratio of PTH(1-84)/ntPTH between treatment groups, patients with lower serum calcium levels, defined as levels <9.5 mg/dl, had higher ratios of PTH(1-84)/ntPTH during therapy for secondary hyperparathyroidism, as has been previously reported [15]. In blood samples in which the serum calcium value was ≥9.5 mg/dl, the ratio of PTH(1-84)/ntPTH was 1.1±0.2; when serum calcium values were <9.5 mg/dl, values of PTH(1-84)/ntPTH were 1.6±0.2 (p<0.05).

Vitamin D dosage

Throughout the course of the study, the average dose of vitamin D sterol in patients receiving doxercalciferol was 4.8±0.6 and 5.1±0.5 μg in the CaCO₃ and sevelamer treatment groups, respectively (NS); the average calcitriol

![Fig. 2](image_url)
dose was $1.4 \pm 0.1$ and $2.3 \pm 0.1 \mu g$ in the CaCO₃ and sevelamer groups, respectively (NS). No differences were found when the dose was normalized by patient weight. The amount of administered vitamin D sterol increased monthly during the first 4 months in response to serum PTH, calcium, and phosphorus levels, reaching stable dosage in the last 4 months of the study at a time when the goal biochemical values were maintained. In order to compare maintenance doses of vitamin D between patients treated with CaCO₃ and those treated with sevelamer, we converted doxercalciferyl dose to a calcitriol equivalent dose (doxercalciferyl dose/5) [20]. During the initial 4 months of the study (the titration phase), there was no difference in the amount of vitamin D sterol administered to patients treated with CaCO₃ versus those receiving sevelamer. However, during the last 4 months of therapy, when doses were stable, CaCO₃-treated patients received $3.5 \pm 0.7 \mu g$/dose, while the sevelamer group received $5.7 \pm 0.7 \mu g$/dose of calcitriol equivalent ($p<0.05$).

Discussion

The results of this analysis indicate that an equivalent degree of PTH reduction and phosphate control was achieved during therapy for secondary hyperparathyroidism when calcitriol or doxercalciferyl, given orally three times per week, was used in conjunction with either CaCO₃ or sevelamer. This reduction in PTH levels occurred despite differences in serum calcium levels and differences in the amount of administered vitamin D sterol. Serum PTH determinations by both 1st PTH-IMAs were higher than those measured by the 2nd PTH-IMA over a wide range of values, with the 2nd PTH-IMA values being 40–60% lower than those obtained by the 1st PTH-IMA; this result is consistent with previous reports [11, 12, 14, 15]. However, there was no difference in the percentage change of PTH by any of the three assays, and final values were similar, regardless of the type of therapy. An equivalent degree of correlation was found between the three assays despite different vitamin D sterol and phosphate binder therapies, similar to the correlation observed between assays during treatment with calcimetics [15]. The ratio of PTH(1-84)/ntPTH did not change throughout the course of the study, and there were no differences observed between the CaCO₃ and sevelamer treatment groups whether patients received calcitriol or doxercalciferyl. However, the average PTH(1-84)/ntPTH ratio was consistently higher in patients with lower serum calcium levels, defined as serum calcium levels <9.5 mg/dl, as has been previously described [15], suggesting either that more PTH(1-84) and/or fewer ntPTH fragments are being generated by the parathyroid gland in these patients.

Although the results of the analysis reported here do not show any differences in the response of different PTH assays to vitamin D sterol and phosphate binder therapy, it is possible that differences may be detectable in a larger patient population. We found no differences in the rates of PTH change, as assessed by the three different assays, from baseline; however, we have previously reported that the current treatment protocol results in a >50% decrease in bone turnover [17]. Thus, the large change in bone formation rate, combined with the lack of difference in PTH assays in the current analysis, suggests that any difference in the prediction of bone by the three assays would likely be of minimal clinical significance.

This study reconfirmed that serum calcium levels increase during therapy with calcium-based binders while remaining unchanged in patients treated with sevelamer [17, 21–23]. In addition, episodes of hypercalcaemia were more frequent in patients receiving therapy with CaCO₃. Indeed, final serum calcium levels in those treated with vitamin D and sevelamer remained unchanged during therapy and were equivalent to those observed in patients treated with calcimimetic agents [15, 24]. Therapy with sevelamer thus allowed for the use of higher doses of vitamin D and may widen the margin of safety of vitamin D therapy by allowing effective control of PTH secretion without inducing hypercalcaemia, a finding which has potential implications in the prevention of vascular calcifications attributed to therapy with active vitamin D sterols [25]. Interestingly, however, the same degree of PTH suppression was observed by all three PTH assays [17], regardless of the type of phosphate-binding agent, the serum calcium levels, and the vitamin D sterol type.

While serum levels of PTH, as measured by both first- and second-generation IMAs (Nichols) have been shown to correlate throughout therapy with calcitriol and CaCO₃ [6], this is the first study to compare the response of the 1st and 2nd PTH-IMAs and the ratio of PTH(1-84)/ntPTH to therapy with different phosphate binders and active vitamin D sterols in patients with secondary hyperparathyroidism. Changes in the ratio of PTH(1-84)/ntPTH is consistent with results from short-term calcium infusion studies [10] as well as with long-term changes associated with the use of calcimimetic agents in hemodialysis patients. Long-term follow-up demonstrated that lower serum calcium concentrations (<9.5 mg/dl) were associated with a greater ratio of PTH(1-84)/ntPTH when compared with serum calcium concentrations >9.5 mg/dl [15]. This difference in the ratio may be attributable to higher PTH(1-84) levels, to lower ntPTH levels, or to a combination of both in patients with lower serum calcium levels. Although in the study reported here we did not detect a difference in serum PTH(1-84) levels based on serum calcium levels, a larger sample size may have revealed some differences in these values. On the
other hand, some ntPTH fragments, such as PTH(7-84), have been shown to bind a receptor other than the PTH/PTHrP receptor and to antagonize the actions of full-length PTH in vivo [7, 8, 10, 26, 27]. Thus, the current data suggest a possible role for ntPTH fragments in parathyroid and bone physiology. However, the clinical relevance of the measurement of these fragments in the assessment and management of secondary hyperparathyroidism remains to be established.

Interestingly, Monier-Faugere et al. recently reported higher values of PTH(1-84) and higher values of the ratio of PTH(1-84)/ntPTH during treatment of adult hemodialysis patients with CaCO3 and intravenous paricalcitol than in those treated with CaCO3 and intravenous calcitriol [16]. The discrepancy between their findings and our results may be due to several factors, such as the differential effects between paricalcitol and doxercalciferol on parathyroid gland secretion, altered bioavailability according to routes of administration (i.e. oral vs. intravenous), differences between adults and children, and/or the specific effect of the type of dialytic modality (hemodialysis vs. peritoneal dialysis). One, or more, of these factors may affect the bioavailability of vitamin D sterols, alter calcium absorption, or change the parathyroid gland’s response to therapy with active vitamin D.

In conclusion, while treatment with both CaCO3 and sevelamer were equally effective in controlling serum phosphorus levels, treatment with CaCO3 resulted in higher serum calcium levels. Higher doses of vitamin D could thus be administered to patients treated with sevelamer, resulting in equivalent suppression of PTH [17], without increases in serum calcium. Two different 1st PTH-IMAs and a 2nd PTH-IMA were suppressed to a similar degree, regardless of therapy. However, lower serum calcium concentrations were associated with higher values for the ratio of PTH(1-84)/ntPTH. Thus, while 2nd PTH-IMAs specifically detect the “biologically active” PTH(1-84) molecule and may provide new insights in parathyroid gland physiology, the data reported here suggest that 1st and 2nd PTH-IMAs are of equal clinical utility for monitoring the response of secondary hyperparathyroidism to treatment with vitamin D analogues and phosphate binders.

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References

1. Quarles LD, Lobaugh B, Murphy G (1992) Intact parathyroid hormone overestimates the presence and severity of parathyroid-mediated osseous abnormalities in uremia. J Clin Endocrinol Metab 75(1):145–150
2. Jüppner H, Potts JT Jr (2002) Immunoassays for the detection of parathyroid hormone. J Bone Miner Res 17 [Suppl 2]:N81–N86
3. Brossard JH, Cloutier M, Roy L, Lepage R, Gascon-Barre M, D’Amour P (1996) Accumulation of a non-(1-84) molecular form of parathyroid hormone (PTH) detected by intact PTH assay in renal failure: importance in the interpretation of PTH values. J Clin Endocrinol Metab 81(11):3923–3929
4. Lepage R, Roy L, Brossard JH, Rousseau L, Dorais C, Lazure C, D’Amour P (1998) A non-(1-84) circulating parathyroid hormone (PTH) fragment interferes significantly with intact PTH commercial assay measurements in uremic patients. Clin Chem 44(4):805–809
5. Boudu P, Ibrahim F, Cormier C, Sarfati E, Souberbielle JC (2006) Unexpected serum parathyroid hormone profiles in some patients with primary hyperparathyroidism. Clin Chem 52(4):757–760
6. Fujimori A, Sakai M, Yoshiya K, Shin J, Kim Ji, Inaba Y, Miyamoto T, Inoue S, Fukagawa M (2004) Bio-intact parathyroid hormone and intact parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism receiving intravenous calcitriol therapy. Ther Apher Dial 8(6):474–479
7. Slatopolsky E, Finch J, Clay P, Martin D, Sicard G, Singer G, Gao P, Cantour T, Dusso A (2000) A novel mechanism for skeletal resistance in uremia. Kidney Int 58(2):753–761
8. Nguyen-Yamamoto L, Rousseau L, Brossard JH, Lepage R, D’Amour P (2001) Synthetic carboxyl-terminal fragments of parathyroid hormone (PTH) decrease ionized calcium concentration in rats by acting on a receptor different from the PTH/PTH-related peptide receptor. Endocrinology 142(4):1386–1392
9. D’Amour P, Brossard JH, Rousseau L, Nguyen-Yamamoto L, Nassif E, Lazure C, Gauthier D, Lavigne JR, Zahradnik RJ (2005) Structure of non-(1-84) PTH fragments secreted by parathyroid glands in primary and secondary hyperparathyroidism. Kidney Int 68(3):998–1007
10. John MR, Goodman WG, Gao P, Cantor TL, Salusky IB, Jüppner H (1999) A novel immunoradiometric assay detects full-length human PTH but not amino-terminally truncated fragments: implications for PTH measurements in renal failure. J Clin Endocrinol Metab 84(11):4287–4290
11. Monier-Faugere MC, Geng Z, Mazow M, Friedler RM, Gao P, Cantor TL, Mailuche HH (2001) Improved assessment of bone turnover by the PTH(1-84)/large C-PTH fragments ratio in ESRD patients. Kidney Int 60(4):1460–1468
12. Salusky IB, Goodman WG, Kuizin BD, Lavigne JR, Zahradnik RJ, Gales B, Wang JJ, Elashoff RM, Jüppner H (2003) Similar predictive value of bone turnover using first- and second-generation immunometric PTH assays in pediatric patients treated with peritoneal dialysis. Kidney Int 63(5):1801–1808
13. Waller SC, Ridout D, Cantor T, Rees L (2005) Parathyroid hormone and growth in children with chronic renal failure. Kidney Int 67(6):2338–2345
14. Coen G, Bonucci E, Ballanti P, Balducci A, Calabria S, Nicolai GA, Fischer MS, Lifrieri F, Manni M, Morosetti M, Moscaritolo E, Sardella D (2002) PTH 1-84 and PTH “7-84” in the noninvasive diagnosis of renal bone disease. Am J Kidney Dis 40(2):348–354
15. Martin KJ, Jüppner H, Sherrard DJ, Goodman WG, Kaplan MR, Nassar G, Campbell P, Curzi M, Charytan C, McCary LC, Guo MD, Turner SA, Bushinsky DA (2005) First- and second-generation immunometric PTH assays during treatment of hyperparathyroidism with cinacalcet HCl. Kidney Int 68(3):1236–1243
16. Monier-Faugere MC, Mawad H, Malluche HH (2007) Opposite effects of calcitriol and paricalcitol on the parathyroid hormone-(1-84)/large carboxy-terminal-parathyroid hormone fragments ratio in patients with stage 5 chronic kidney disease. Clin J Am Soc Nephrol 2(6):1255–1260
17. Salusky IB, Goodman WG, Sahney S, Gales B, Perilloux A, Wang HJ, Elashoff RM, Jüppner H (2005) Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. J Am Soc Nephrol 16(8):2501–2508
18. Salusky IB, Coburn JW, Brill J, Foley J, Slatopolsky E, Fine RN, Goodman WG (1988) Bone disease in pediatric patients undergoing dialysis with CAPD or CCPD. Kidney Int 33(5):975–982
19. Parfitt AM, Drezner MK, Glorieux FH, Kanis JA, Malliche H, Meunier PJ, Ott SM, Recker RR (1987) Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res 2(6):595–610
20. Upton RA, Knutson JC, Bishop CW, LeVan LW (2003) Pharmacokinetics of doxercalciferol, a new vitamin D analogue that lowers parathyroid hormone. Nephrol Dial Transplant 18(4):750–758
21. Chertow GM, Burke SK, Raggi P (2002) Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 62(1):245–252
22. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P (2005) Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 68(4):1815–1824
23. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM (2007) Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 71(5):438–441
24. Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Herz G, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCary LC, Zani VJ, Olson KA, Drueke TB, Goodman WG (2004) Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 350(15):1516–1525
25. Milliner DS, Zinsmeister AR, Lieberman E, Landing B (1990) Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int 38(5):931–936
26. Liu BY, Guo J, Lanske B, Divieti P, Kronenberg HM, Brinthurst FR (1998) Conditionally immortalized murine bone marrow stromal cells mediate parathyroid hormone-dependent osteoclastogenesis in vitro. Endocrinology 139(4):1952–1964
27. D’Amour P, Rakel A, Brossard JH, Rousseau L, Albert C, Cantor T (2006) Acute regulation of circulating parathyroid hormone (PTH) molecular forms by calcium: utility of PTH fragments/PTH(1-84) ratios derived from three generations of PTH assays. J Clin Endocrinol Metab 91(1):283–289