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Treatment Protocol for Controlling Bone Metabolism Parameters in Hemodialysis Patients

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1. Introduction

Abnormal mineral metabolism and severe secondary hyperparathyroidism play a key role in the pathophysiology of skeletal and extraskeletal calcification and are associated with increased morbidity and mortality among hemodialysis (HD) patients (Block GA et al., 1998, 2004; Ganesh et al., 2001; London GM et al., 2003). As a result of these findings, the National Kidney Foundation introduced guidelines in 2003 on controlling parathyroid hormone (PTH), calcium (Ca), phosphorous (P) and calcium-phosphorous ion product (CaxP) in these patients (National Kidney Foundation-Kidney Disease Outcomes and Quality Initiative, 2003). However, in spite of the publication of the K/DOQI guidelines, most HD patients remained outside the recommended targets (Al Aly et al., 2004; Arenas et al., 2006; Lorenzo et al., 2006; Maduell et al., 2005). Historically, Ca-containing phosphate binders and vitamin D have provided the main strategies for reducing P and PTH levels (Slatopolsky et al., 1986). However, the overuse of Ca-containing phosphate binders and active vitamin D can result in hypercalcemia, high CaxP level and Ca overload, which may accelerate vascular disease and hasten death. These side effects potentially require temporary cessation of vitamin D and a reduction in Ca-containing binder administration. This cycle results in a temporary worsening of secondary hyperparathyroidism, allowing bone disease progression (Block et al., 1998, 2000; Johnson et al., 2002; Moe et al., 2003). Hence, new treatment strategies are required (Jindal et al., 2006; Moe et al., 2009;).

Since 2006, two new drugs, paricalcitol and cinacalcet, have been available in daily clinical practice for secondary hyperparathyroidism treatment. Paricalcitol is a vitamin D metabolite that has some advantages over calcitriol, the standard form of vitamin D used worldwide. Paricalcitol suppresses PTH faster than calcitriol (Sprague et al., 2001), and may have a lesser Ca and P intestinal absorption capacity, with smaller increases in Ca and P serum (Llach et al., 2001). Patients who receive paricalcitol may also have a significant survival advantage over those who receive calcitriol (Teng et al., 2003). Despite these advantages, the occurrence of hypercalcemia and high CaxP, when high doses of paricalcitol are used, is not unusual (Goodman, 2001; Martin & Gonzalez, 2001).

Cinacalcet, the first calcimimetic available, has provided a new approach for severe secondary hyperparathyroidism. It increases the sensitivity of the Ca-sensing receptor on the parathyroid cell surface to extracellular Ca ions, thereby inhibiting the release of PTH. All clinical trials concluded that cinacalcet is effective in reducing PTH while simultaneously lowering Ca, P and CaxP levels in HD patients (Block et al, 2004; Goodman et al., 2002; Lindberg et al., 2005; Quarles et al., 2003). All these effects could facilitate achievement of the K/DOQI recommended targets (Block et al., 2008; Messa et al, 2008; Moe et al., 2005).

Given the difficulty of achieving K/DOQI targets, and the absence of treatment algorithms that take into account both drug treatment (conventional drugs like phosphate binders, and new drugs like paricalcitol and cinacalcet) and HD features, such as the length of dialysis session or the dialysate Ca concentration recommended, our HD Unit has, since 2006, implemented a new treatment protocol for controlling bone metabolism parameters. The aim of our study was to evaluate the long-term effect of applying this protocol on achieving K/DOQI targets.

2. Materials and methods

2.1 Study design

This is a single-centre, intervention study. HD patients were eligible for inclusion if they were adults (age ≥ 18 years) and if they had attended our HD unit for at least 3 months from Jan 2006 to April 2008. Patients who had been on HD therapy for less than 3 months, or who presented excessively suppressed parathyroid hormone (PTH < 10 pg/mL) secondary to previous parathyroidectomy, were excluded. Starting in April 2006, the new protocol treatment was applied to 52 of the 57 patients attending our unit over this two year period. Five patients were excluded (in every case because of a stay in our HD unit of less than 3 months).

2.2 Interventions

This intervention study consisted of three stages: an assessment stage 3 months before applying the protocol (base period), and the 12 and 24 month effectiveness assessment phases. During the base period (January-March 2006), calcitriol was the only drug available for hyperparathyroidism treatment, and a bath containing 2.5 mEq/L of Ca was preferentially used, as K/DOQI guidelines recommended. Since April 2006, treatment for control bone metabolism parameters, including cinacalcet administration, has been adjusted according to our new protocol. All patients treated with calcitriol, were changed to paricalcitol. Dialysate Ca content was determined individually, based on the protocol. In all three stages, Ca acetate was the only Ca-containing phosphate binder used, in order to limit the total dosage of elemental Ca provided. The preferred non-Ca phosphate binder used was sevelamer, up to a maximum dose of 4800 mg per day. Only if P remained > 5.5 mg/dL, in spite of full doses of Ca acetate and sevelamer, was treatment with aluminium hydroxide considered. In line with K-DOQI guidelines, we tried to maintain serum Ca levels within the normal range for our laboratory (8.4-10.2 mg/dL), and preferably towards the lower end (8.4-9.5 mg/dL); P below 5.5 mg/dL; CaxP below 55 mg²/dL²; and PTH levels between 150 and 300 pg/mL. The protocol consisted in three treatment algorithms, depending on the PTH level. When parathyroid hormone level was less than 150 pg/mL (Figure 1), depending on Ca levels, the dose of cinacalcet or paricalcitol was reduced gradually, until a minimum dose (oral cinacalcet, 30 mg three times per week; intravenous paricalcitol, 2.5 μ g once per

week) was reached. If PTH levels continued to be oversuppressed, we considered a reduction in dialysate Ca concentration from 3.0 to 2.5 mEq/L or a reduction in the dose of Ca acetate, in order to stimulate the PTH secretion.

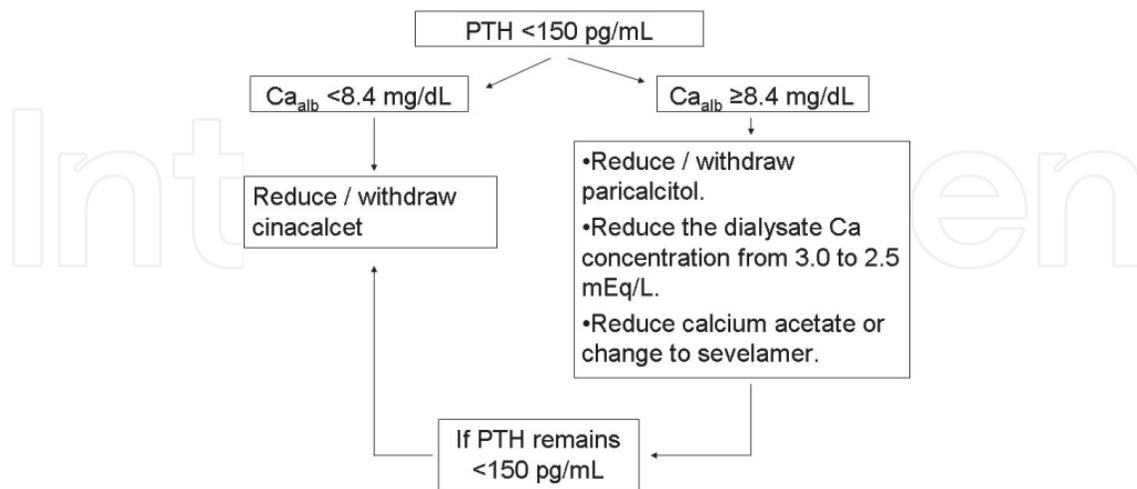


Fig. 1. Algorithm treatment when parathyroid hormone level was less than 150 pg/mL.

When parathyroid hormone level was within the target range (Figure 2), osteodystrophy treatment was modified according to Ca and P levels. If Ca levels ≥ 9.5 mg/dL and P levels were within the range, the doses of paricalcitol or Ca acetate were reduced. A reduction in dialysate calcium concentration to 2.5 mEq/L was also considered. If P levels were > 5.5 mg/dL and Ca levels were within the range, we increased the dose of phosphate binders and we considered lengthening the time of dialysis session. If both Ca and P levels were too high, Ca acetate was replaced by non-Ca phosphate binders and paricalcitol dosage was reduced or replaced by cinacalcet. In this case, we also considered a reduction in dialysate Ca concentration to 2.5 mEq/L and an increase in the length or frequency of dialysis session.

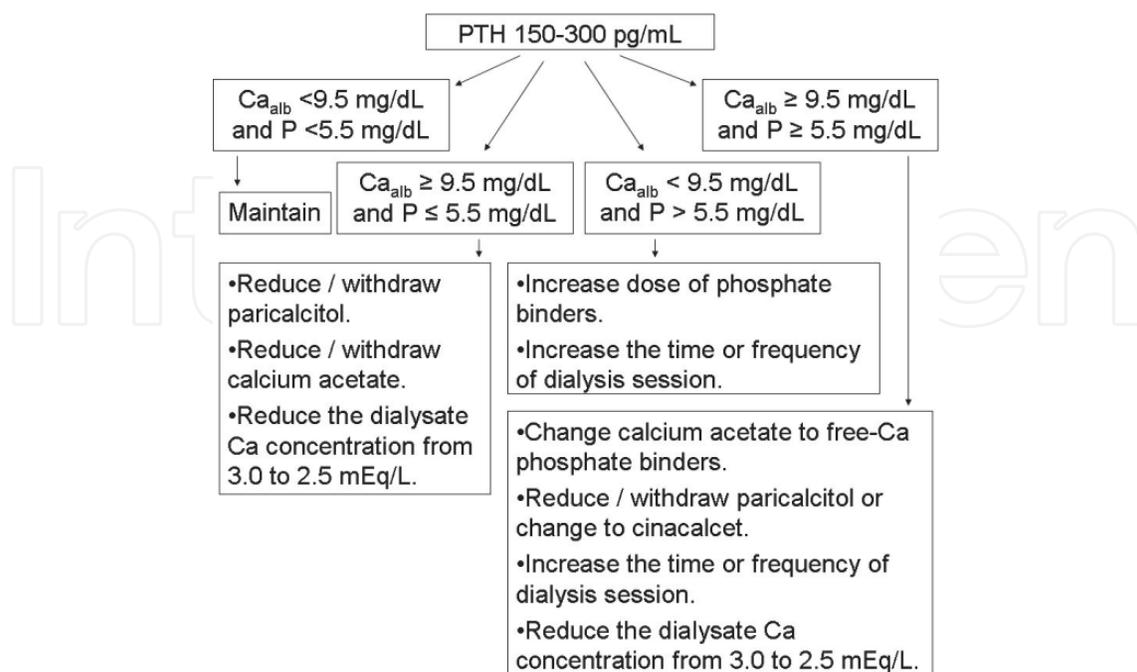


Fig. 2. Algorithm treatment when parathyroid hormone level was within the target range.

When parathyroid hormone was over 300 pg/mL (Figure 3), and Ca <9.5 mg/dL, dialysate Ca concentration were raised from 2.5 to 3.0 mEq/L, and we increased paricalcitol or cinacalcet, depending on whether the P and CaxP levels were normal or too high, respectively. Increases in the length of dialysis session and in the Ca acetate dosage were also considered. When Ca levels were between 9.5 to 10.2 mg/dL and CaxP <55 mg²/dL², cinacalcet was preferentially used. If PTH remained too high, in spite of full doses of cinacalcet, we considered changing Ca acetate to sevelamer and increasing dialysate Ca concentration or adding low doses of paricalcitol, carefully monitoring CaxP levels. When Ca levels were too high or within the high-normal range and CaxP >55 mg²/dL², paricalcitol was reduced or withdrawn and the cinacalcet dosage was increased. We also considered increasing the length or frequency of dialysis session and the dosage of non-Ca phosphate binders, and reducing the dialysate Ca concentration.

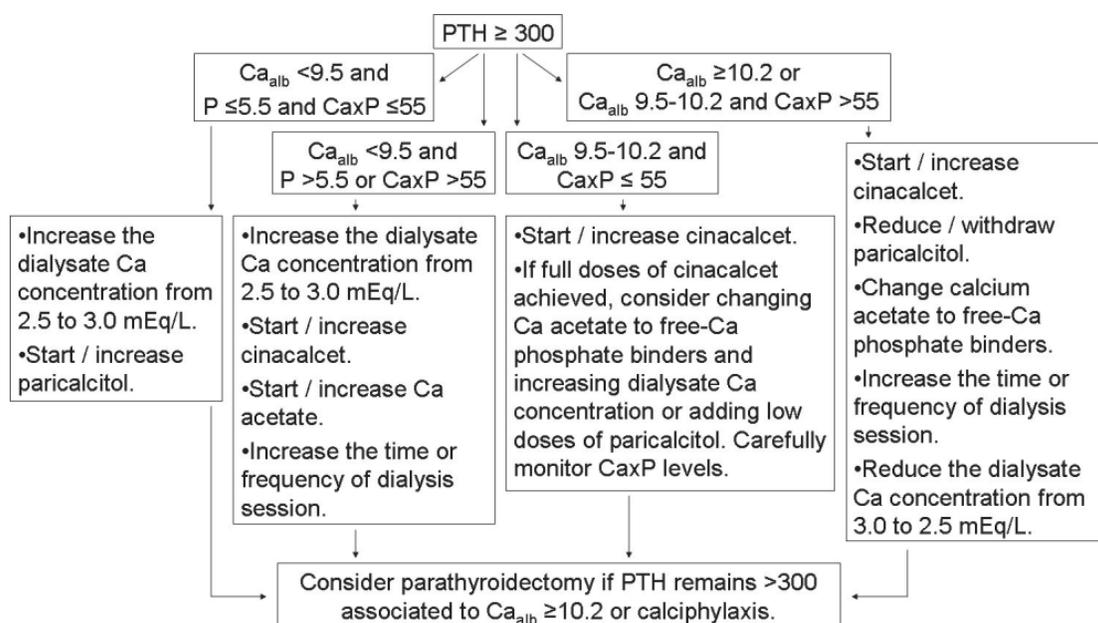


Fig. 3. Algorithm treatment when parathyroid hormone was over 300 pg/mL.

2.3 Laboratory tests

All blood samples were collected at the start of the dialysis session following the longest interdialysis period. The samples were analyzed for serum Ca, P and intact PTH. All K-DOQI parameters were measured at least monthly. In total, 863 blood samples were analyzed (median: 16.9 samples per patient). Total serum Ca and P were measured by colorimetric assay (Roche Diagnostics GmbH, Mannheim, Germany), the reference value for serum calcium being 8.6–10.4 mg/dL and for phosphate 3.5–5.5 mg/dL. The serum levels of total Ca were adjusted for circulating albumin levels (reference values: 3.4–4.8 g/dL). Albumin levels were assessed by Albumin BCG Method (Roche Diagnostics GmbH, Mannheim, Germany). PTH levels were assessed by an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics GmbH, Mannheim, Germany). The reference range for healthy adults is 15–65 pg/mL.

2.4 Renal replacement therapy

Patients received standard HD or post-dilution hemodiafiltration (HDF) treatment, lasting between 3h and 4h30m, three times per week. Dialysis prescription was monitored to

maintain $Kt/V > 1.2$. Polysulphone or AN69st membrane dialysers were used. Blood flow was at least 300 mL/min and dialysate flow 750 mL/min. Dialysate composition was Ca 2.5 or 3.0, Na 139 or 140, K 1.5 or 1.9, bicarbonate 34, 37 or 40.8, mEq/L. Infusate composition for patients on HDF was Na 145, Cl 85, bicarbonate 60 mmol/L, with an infusion flow of 2 L/hour. The dialysis equipment employed was Bellco® or Hospal®.

2.5 Statistics

Student's unpaired *t*-test was used to compare the three phase means of all PTH, Ca, P and CaxP values. The proportion of patients within K/DOQI target ranges over the 2 years following the implementation of the protocol was used to evaluate effectiveness. Percentages were compared using the chi-square test. We analyzed potential factors involved in the evolution of bone metabolism parameters, such as phosphate binder dosage, the cinacalcet and paricalcitol used, and the features of HD employed. Results are expressed as mean and standard deviation. A multivariate analysis of the factors associated with the achievement of all four K/DOQI target ranges during the last year were assessed using logistic regression analysis. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1 Patients

Fifty-two patients were studied, twenty-nine men and twenty-three women, 66.7 ± 17.7 years old (range, 25 to 86 years) with a mean time on HD therapy of 71 ± 84 months (range, 4 to 318 months). The etiology of renal failure was hypertensive nephrosclerosis ($n=12$), diabetic nephropathy ($n=10$), glomerulonephritis ($n=9$), interstitial nephritis ($n=8$), polycystic kidney disease ($n=2$), Alport's syndrome ($n=1$), and undetermined ($n=10$). The demographics of the patients studied at each stage of the study are summarized in Table 1. Mean observation time was 16.7 ± 9.4 months.

	Baseline	1 year	2 years
Number of patients dialysed	30	36	43
Number of prevalent patients	25	28	30
Number of incident patients	5	8	13
Mean age of patients (years)	67.7 ± 16.9 (25 - 84)	67.2 ± 17.3 (25 - 85)	66.6 ± 16.4 (31 - 86)
Mean time on HD (months)	113 ± 89 (12 - 294)	94 ± 89 (6 - 306)	70 ± 86 (3 - 318)
Mean serum albumin (g/dL)	3.8 ± 0.3 (3.5 - 4.6)	3.8 ± 0.3 (2.8 - 4.6)	3.7 ± 0.4 (2.5 - 4.6)
% of diabetic patients	20% (6)	17% (6)	26% (11)

Table 1. Demographic characteristics of patient population at each stage of the study.

3.2 Evolution of biochemical parameters

Changes in the adjusted Ca (Ca_{Alb}), P, CaxP, and PTH levels before and after implementing the protocol are shown in Table 2. Ca_{Alb} , CaxP and PTH levels decreased significantly throughout the study, with a mean decrease of 3.5% ($p=0.016$), 8.2% ($p=0.023$) and 39.4% ($p=0.002$), respectively. Although there was a reduction in P levels, the difference did not reach statistical significance ($p=0.075$).

	Baseline	1 year	2 years	<i>p</i>
Ca _{Alb} (mg/dL)	9.46 ± 0.57 (8.26 - 10.45)	9.20 ± 0.529 (7.54 - 10.24)	9.13 ± 0.56 (7.35 - 10.40)	0.016
P (mg/dL)	4.97 ± 1.09 (3.29 - 7.91)	4.62 ± 0.94 (3.02 - 6.7)	4.56 ± 0.84 (3.05 - 6.79)	0.075
CaxP (mg ² /dL ²)	47.36 ± 11.33 (29.97 - 79.81)	42.58 ± 9.03 (27.10 - 63.26)	41.65 ± 8.27 (26.91 - 65.52)	0.023
PTH (pg/mL)	343 ± 209 (11 - 864)	239 ± 126 (36 - 678)	208 ± 107 (42 - 704)	0.002

Table 2. Evolution of Biochemical Parameters.

Mean corrected calcium, serum phosphorus, ion calcium-phosphorus product, and intact parathyroid hormone levels at each stage of the study were compared using Student's unpaired *t*-test.

3.3 Achievement of K/DOQI target levels

The percentages of patients achieving the K/DOQI targets are summarized in Figure 4. In the base period, the proportion of patients achieving P, CaxP and PTH targets were 67%, 73% and 13% respectively. An improvement in the achievement of these three targets was observed, reaching 84%, 93% and 72% of patients, respectively. This improvement was significant in CaxP and PTH levels ($p=0.024$ and $p<0.001$, respectively). The increase in the percentage of patients achieving P target did not reach statistical significance ($p=0.074$). The proportion of patients achieving Ca_{Alb} levels remained above 90% throughout the study ($p=0.644$). Overall, the rate of patients with all four K-DOQI parameters within target ranges improved significantly from 10.0 at baseline, to 33.3% ($p=0.023$) and to 60.5% ($p<0.001$) during the first and second year after implementing the protocol, respectively (Figure 5).

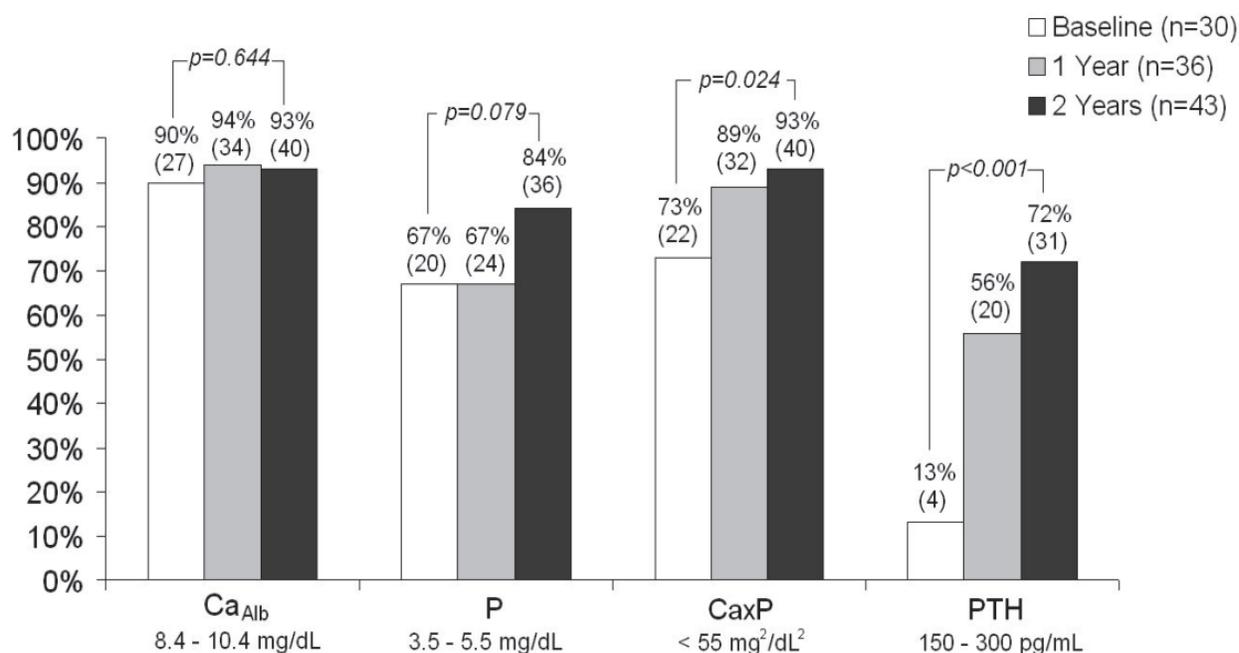


Fig. 4. Percentage (%) of patients achieving each K/DOQI target by time period.

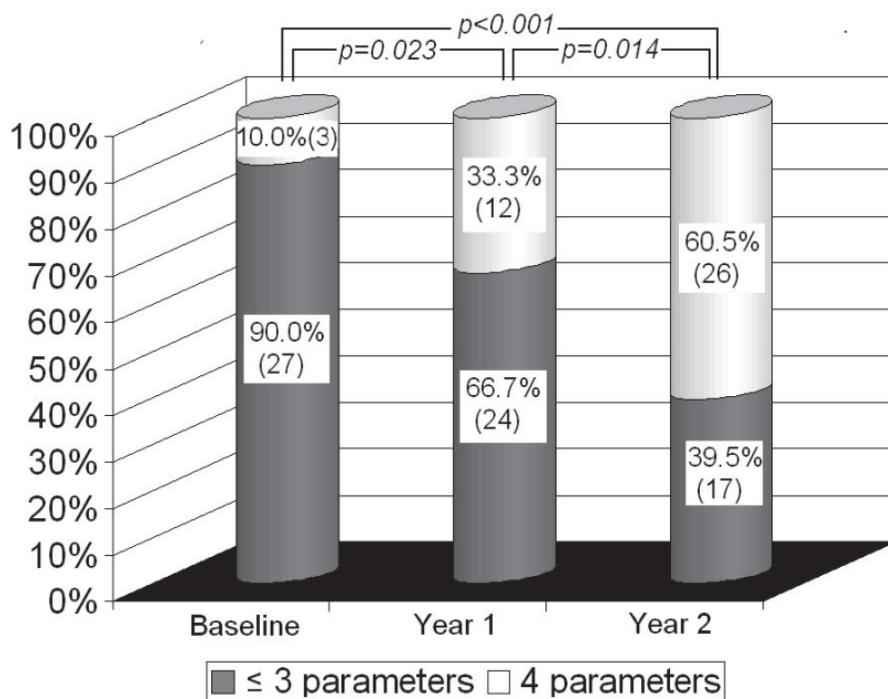


Fig. 5. Percentage (%) of patients achieving all four K/DOQI targets by time period.

3.4 Medication use

Treatment of osteodystrophy over time is shown in Table 3. As the protocol stated, all patients treated with calcitriol were changed to paricalcitol, which was administered to approximately a third of the patients throughout the study. Cinacalcet was the other drug available for HPT, and was administered to 22% and 26% of patients during the first and second year after implementing the protocol, respectively. Two drugs were administered in combination to 5 (12%) and 6 (14%) patients in each assessment stage. Ca acetate was the only calcium-based phosphate binder used, and the proportion of patients receiving this drug remained unchanged (70% of patients, approximately). The mean total dosage of elemental calcium provided by calcium acetate increased from 451 ± 151 to 562 ± 275 mg/day without statistical significance ($p=0.079$). The proportion of patients under treatment with aluminium hydroxide at the start of the study was significantly reduced from 20% ($n=6$) to 5% ($n=2$) ($p=0.047$). Its dose remained unchanged throughout the study.

Mean total dosage of calcium acetate is expressed as elemental calcium provided by calcium acetate. Mean doses were compared using Student's unpaired *t*-test. Percentages were compared using the chi-square test. Abbreviations: n: number of patients; n.a.: not applicable. †Mean dose of aluminium hydroxide cannot be computed because the standard deviations of both groups were 0.

3.5 Renal replacement therapy

Changes in HD features over time are shown in Table 4. After implementing the protocol, a 3.0 mEq/L dialysate Ca concentration became the most widely used (7% vs. 72%; $p=0.001$), and a significant increase in the proportion of patients under convective therapy was detected (30% vs. 67%; $p=0.034$). The length of dialysis session and the HD dose remained unchanged.

	Baseline (n=30)	1 year (n=36)	2 years (n=43)	<i>p</i>
Rocaltrol n, (%) patients on treatment mean dose ($\mu\text{g}/\text{week}$)	13 (43%) 1.44 ± 0.21 (0.75 - 1.50)	-	-	n.a. n.a.
Paricalcitol n, (%) patients on treatment mean dose ($\mu\text{g}/\text{week}$)	-	16 (44%) 9.93 ± 5.19 (2.50 - 22.50)	14 (33%) 9.38 ± 4.87 (5.00 - 20.00)	n.a. n.a.
Cinacalcet n, (%) patients on treatment mean dose (mg/day)	-	8 (22%) 35.7 ± 17.8 (15 - 60)	11 (26%) 45.0 ± 34.6 (15 - 120)	n.a. n.a.
Calcium acetate n, (%) patients on treatment mean dose (mg/day)	20 (67%) 451 ± 151 (254 - 762)	28 (78%) 553 ± 242 (127 - 1143)	28 (65%) 562 ± 275 (127 - 1143)	0.547 0.079
Sevelamer n, (%) patients on treatment mean dose (mg/day)	20 (67%) 4760 ± 1916 (2400 - 7200)	22 (61%) 4255 ± 1645 (2400 - 7200)	26 (61%) 4062 ± 1662 (800 - 7200)	0.386 0.179
Aluminium hydroxide n, (%) patients on treatment mean dose (mg/day)	6 (20%) 699 ± 0 (699 - 699)	2 (6%) 699 ± 0 (699 - 699)	2 (5%) 699 ± 0 (699 - 699)	0.047 †

Table 3. Treatment of osteodystrophy at each stage of the study.

	Baseline (n=30)	1 year (n=36)	2 years (n=43)	<i>p</i>
Dialysate Ca concentration, n (%)				
Patients with Ca 2.5	28 (93%)	6 (17%)	12 (28%)	0.001
Patients with Ca 3.0	2 (7%)	30 (83%)	31 (72%)	
Dialysis type, n (%)				
Hemodialysis	21 (70%)	11 (31%)	14 (33%)	0.034
Hemodiafiltration	9 (30%)	26 (69%)	29 (67%)	
Length of dialysis session (hours/week)	11.2 ± 1.3 (9.0 - 13.5)	11.4 ± 1.3 (9.0 - 13.5)	11.6 ± 1.3 (9.0 - 13.5)	0.481
Kt/V	1.39 ± 0.24 (0.90 - 1.84)	1.50 ± 0.20 (1.10-1.91)	1.42 ± 0.22 (1.01-1.90)	0.439

Table 4. HD features at each stage of the study.

Student's unpaired *t*-test was used to compare means of length of dialysis session and Kt/V values. Percentages were compared using the chi-square test. Abbreviations: n: number of patients; URR: urea reduction ratio.

3.6 Factors associated with achieving K/DOQI targets

Data on each group of patients within and outside all four K/DOQI target ranges during the last year were compared (Table 5). The use of cinacalcet (39% vs. 6%; $p=0.017$) and the use of a 3.0 mEq/L dialysate Ca concentration (85% vs. 53%; $p=0.028$) were significantly more frequent in the group of patients who achieved all K/DOQI targets than in the group

	≤ 3 K/DOQI targets achieved (n=17)	All 4 K/DOQI targets achieved (n=26)	<i>p</i>
Gender, n (%)			
Female	9 (53%)	10 (39%)	0.267
Male	8 (47%)	16 (61%)	
Age (years)	67.98 ± 15.88	65.62 ± 17.03	0.650
Mean time on HD (months)	50.21 ± 55.56	82.17 ± 100.22	0.756
Diabetes mellitus, n (%)	6 (35%)	5 (19%)	0.493
Mean serum albumin (g/dL)	3.69 ± 0.41	3.76 ± 0.36	0.575
Mean 25 OH vit D (ng/mL)	11.9 ± 4.5	12.4 ± 4.5	0.770
Dialysate Ca concentration, n (%)			
Patients with Ca 2.5	8 (47%)	4 (15%)	0.028
Patients with Ca 3.0	9 (53%)	22 (85%)	
Dialysis type, n (%)			
Hemodialysis	7 (41%)	7 (27%)	0.259
Hemodiafiltration	10 (59%)	19 (73%)	
Length of dialysis session (hours/week)	11.4 ± 1.4	11.5 ± 1.2	0.434
Kt/V	1.37 ± 0.22	1.46 ± 0.21	0.178
Residual diuresis†, n (%)	3 (18%)	7 (27%)	0.375
Paricalcitol			
n, (%) patients on treatment	4 (24%)	10 (39%)	0.247
mean dose (µg/week)	8.13 ± 4.73	9.79 ± 5.05	0.573
Cinacalcet			
n, (%) patients on treatment	1 (6%)	10 (39%)	0.017
mean dose (mg/day)	30	46.7 ± 36.6	0.909
Calcium acetate			
n, (%) patients on treatment	11 (65%)	17 (65%)	0.608
mean dose (mg/day)	577 ± 323	553 ± 250	0.434
Sevelamer			
n, (%) patients on treatment	10 (39%)	16 (62%)	0.554
mean dose (mg/day)	4000 ± 1131	4100 ± 1957	0.870
Aluminium hydroxide			
n, (%) patients on treatment	2 (12%)	0 (0%)	0.151

Table 5. Characteristics of the patients who achieved all K/DOQI target ranges during the second year period and those who did not. Mean total dosage of calcium acetate is expressed as elemental calcium provided by calcium acetate. Student's unpaired *t*-test was used to compare means. Percentages were compared using the chi-square test. Abbreviation: n, number of patients; 25 OH vit D, 25-Hydroxyvitamin D; URR, urea reduction ratio. † Residual diuresis is defined as diuresis >1000 mL/24h and residual KtV ≥0.4.

outside ranges. Although there was a higher proportion of patients under paricalcitol treatment (39% vs. 24%) and convective therapy (73% vs. 59%) in the group achieving all targets, the differences did not reach statistical significance ($p=0.247$ and $p=0.259$, respectively). There were no differences in the use of phosphate binders or the dialysis dose. A multivariate analysis found that the use of a 3.0 mEq/L dialysate Ca concentration (OR 5.756; 1.102-30.077; $p=0.038$) and treatment with cinacalcet (OR 12.684; 1.115-144.352; $p=0.041$) were the factors associated with achieving all K/DOQI targets.

4. Discussion

In spite of applying the K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease, achievement of K/DOQI targets remains difficult. In 2006, coinciding with the availability in daily clinical practice of paricalcitol and cinacalcet, our HD Unit implemented a new treatment protocol for controlling the bone metabolism parameters better. As Figures 1, 2 and 3 show, this protocol consisted of three practical treatment algorithms, based on the use of cinacalcet and paricalcitol and the individualization of the dialysate Ca concentration employed, as the main strategies for hyperparathyroidism control, and of dialysis adequacy and combined therapy with sevelamer and Ca acetate for controlling Ca and P levels. Although other algorithms for controlling bone metabolism parameters have been developed (Cannata & Drueke, 2000; Messa et al, 2008; Torregrosa et al., 2011), this, we believe, is the first one to take into account both the drug treatment and HD features, such as the length of dialysis session or the dialysate Ca concentration recommended.

Application of this new treatment protocol was effective and resulted in significant reductions in mean Ca_{Alb} , CaxP and PTH levels (Table 2), with a higher proportion of patients achieving the recommended goals. Noteworthy is the 60.5% of patients with all four K-DOQI parameters within target ranges in the second year after implementing the protocol (Figure 5). This improvement in K/DOQI targets maintained over time could have a direct impact in the survival of patients, given that the simultaneous control of all bone and mineral metabolisms have been showed to be associated with improved survival (Danese et al., 2008).

Implementation of the protocol entailed the administration of paricalcitol and cinacalcet, a preferential use of convective therapies, and the most widely used dialysate Ca concentration of 3.0 mEq/L (Tables 4 and 5). However, it is not easy to assess which of the measures carried out, following implementation of the protocol, has the greatest effect on improving the K/DOQI targets observed, given the multiple factors involved in PTH secretion and in Ca and P levels. We, therefore, compared the characteristics of the patients who achieved all K/DOQI target ranges during the second year of study and those who did not (Table 5). Although there was higher HD dose and a higher proportion of patients under paricalcitol treatment and convective therapy in the group within all the targets, a multivariate analysis showed that the use of a 3.0 mEq/L dialysate Ca concentration and the treatment with cinacalcet were the only two factors significantly associated with achievement of all K/DOQI targets.

These findings are consistent with the literature. Cinacalcet, the first calcimimetic available in daily clinical practice, has proven effective for lowering PTH, Ca, P and CaxP

levels in HD patients (Block et al, 2004; Goodman et al., 2002; Lindberg et al., 2005; Quarles et al., 2003). This ability to lower PTH, while limiting the risks of hyperphosphatemia or hypercalcemia, has improved the achievement of the proposed treatment goals (Block et al., 2008; Messa et al., 2008; Moe et al., 2005), allowing it to be used synergistically in combination with vitamin D sterols (Chertow et al., 2006; Messa et al., 2008). Our protocol took this favourable and complementary effect of combined treatment into account: 60% of the patients who were on paricalcitol treatment and achieved all K/DOQI goals during the second year of study, also received treatment with cinacalcet. In conclusion, we cannot explain the great improvement in K/DOQI goals achieved throughout the study without the use of cinacalcet, either alone or in association with paricalcitol. It's to note the absence of significant association between the use of paricalcitol and achievement of control of all K/DOQI targets. We think it might be related to the fact that 43% of the patients were previously treated with calcitriol. Hence it's difficult to detect any advantages in improving bone metabolism parameters with the use of paricalcitol. Despite these results, we still recommend the preferential use of paricalcitol over calcitriol, given the benefits observed in other studies with the selective vitamin D receptor activation (Llach et al., 2001; Sprague et al., 2001; Teng et al., 2003).

Greater use of a 3.0 mEq/L dialysate Ca concentration was the other factor significantly associated with achieving all K/DOQI targets (85% of patients within all targets). Although optimal dialysate Ca concentration for HD patients has been set at 2.5 mEq/L according to K-DOQI guidelines, this recommendation is opinion-based and could negatively affect secondary hyperparathyroidism (Argilés et al., 1998; Fernández, et al., 1995). Several studies have reported better control of secondary hyperparathyroidism, without risk of severe hypercalcemia, after raising the dialysate Ca concentration from 2.5 to 3.0 mEq/L (Argilés, 1995; Malberti & Raviani, 2004; Molina et al., 2008). A Ca concentration of 3.0 mEq/L has, therefore, been suggested as the first choice for the majority of patients on HD (Cannata & Drueke, 2000; Torregrosa et al, 2011; Touissant et al., 2006). In any case, the best approach would be to individualize the prescription of dialysate Ca concentration, as the K-DOQI guidelines noted.

Noteworthy is the absence of significant changes observed in the use of phosphate binders, with the exception of aluminium hydroxide, the use of which was significantly reduced, as evidence of better control of bone metabolism parameters. Although the proportion of patients receiving Ca acetate remained unchanged, the mean total dosage of elemental Ca provided showed a tendency to increase (451 ± 151 vs 562 ± 275 mg/day; $p=0.079$). The lack of statistical significance could be due to the limited number of patients. This raise in Ca provided by Ca-containing phosphate binders has been previously reported in another study with cinacalcet therapy (Block et al., 2008), where excessively high doses of Ca provided by binders were necessary in order to avoid hypocalcemia. In our study, however, the mean total dosage of elemental Ca provided remained below the maximum dose recommended by K/DOQI guidelines. We speculate that the relatively small average dose of cinacalcet used (45.0 ± 34.6 mg/day), the preferential use of a dialysate Ca concentration of 3.0 mEq/L and the administration of paricalcitol could explain the absence of the need for excessively high doses of Ca acetate. Finally, we should emphasize the desirability of only using Ca acetate, as the Ca-

containing phosphate binder, in order to limit the total dosage of elemental Ca provided.

The current study has several limitations. This was an intervention study without a control group. It would have been interesting to study additional markers of bone metabolism such as bone mass, skeletal fracture rates, cardiovascular calcification or arterial function, given that they could provide more valuable information on the overall assessment of renal bone disease than K-DOQI core measurement standard biomarkers. Other limitations of our study were the limited number of patients, which is common in a single-centre study. However, this was compensated for by the long follow-up period and the relatively high number of blood samples analyzed.

5. Conclusion

Two years after its implementation, the proposed treatment protocol for control bone metabolism parameters has greatly increased the achievement of K/DOQI treatment targets in most of the HD patients. The protocol entailed the administration of cinacalcet, the replacement of calcitriol by paricalcitol, and the incorporation of individual dialysate Ca concentration prescriptions into the algorithm, with a preferential use of a dialysate Ca concentration of 3.0 mEq/L.

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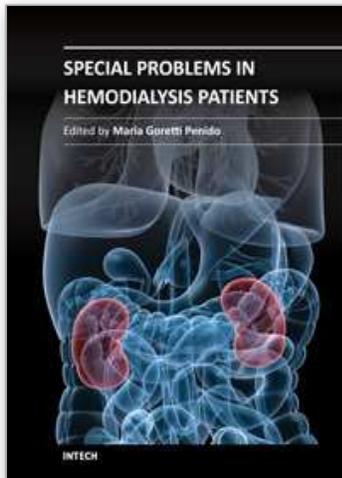
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