Low-calcium peritoneal dialysis solution is effective in bringing PTH levels to the range recommended by current guidelines in patients with PTH levels < 150 pg/dL

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Abstract

Introduction/objective: Adinamic bone disease (ABD) is a common finding in peritoneal dialysis (PD) and is associated with higher risk of developing cardiovascular and bone disease. Data from BRAZPD indicates that 3.5 mEq/L calcium PD solutions represents the majority of PD prescriptions in the country. A positive calcium balance can contribute to ABD development. Currently guidelines suggest that PTH-i levels in end stage renal disease should be kept from 150-300 pg/mL. The purpose of this study is to evaluate 6 month PTH-i response after conversion to 2.5 mEq/L calcium PD solution in patients with baseline PTH-i levels < 150 pg/mL. **Methods:** Prospective, observational study of all prevalent patients (at least 90 days on therapy) on PD of a single Brazilian center from January 2008 to May 2009. Inclusion criteria (1) be in use of a PD solution with 3.5mEq/L of calcium; (2) baseline PTH leves < 150 pg/mL. According to clinical practice patients could be switched to PD solutions with 2.5 mEq/L of calcium. **Results:** 35 patients (age 62 ± 17 years) were included. Of these 22 were converted to 2.5 mEq/L calcium solutions. Diabetic nephropathy (36%) was the main cause of renal disease followed by nephrosclerosis (25%) and glomerulonephritis (14%). Converted group presented a greater increase in PTH levels when compared with the control group (Δ194 pg/dL *versus* Δ 92/dL; p < 0,05). Among patients switched to low calcium solution, 41% reached the target values (PTH 150-300 pg/mL) compared to 14% whose remain with normal calcium solutions (p < 0.05). There were no differences between groups regarding calcium, phosphorus and alkaline phosphatase. **Conclusion:** In patients with PTH < 150 pg/mL conversion to low calcium solutions (2.5 mEq/L) appears to be a simple and effective strategy to bring PTH levels to the range determined by current guidelines when compared with 3.5mEq/L calcium PD solutions.

Keywords: peritoneal dialysis, dialysis solutions, calcium, parathyroid hormone.

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Introduction

Mineral bone metabolism disorders are often observed in patients with chronic kidney disease (CKD), even at the initial stages.[1] Recently, the classification has been standardized to Chronic Kidney Disease Bone Mineral Disorders (CKD-BMD), a concept that encompasses clinical biochemical and bone alterations, as well as information on cardiovascular calcification.[2]

The adynamic bone disease (ABD) is one form of presentation of this disorder that presents a high prevalence in peritoneal dialysis (PD) and is associated with a higher risk of cardiovascular disease and fractures.[3] Histologically, ABD is characterized by low bone remodeling, a reduced number of osteoblasts and osteoclasts, absence of aluminum deposition and normal or reduced osteoid thickness.[2,4,5] The causes currently involved in the development of ABD are attributed to a continuous positive balance of calcium with the use of calcium-based oral chelating agent for the treatment of hyperphosphatemia, as well as the use of dialysis solutions at supraphysiological calcium concentrations, the incorrect and abusive use of vitamin D, hyperglycemia, aluminum intoxication, older age, systemic inflammation and malnutrition.[5-9]

In Brazil, according to data from the Brazilian Peritoneal Dialysis Multicenter Study (BRAZPD), the calcium solutions at 2.5 mEq/L are seldom used in daily clinical practice. The use of a solution with a calcium concentration of 3.5 mEq/L, which is predominant in the country, promotes a positive calcium balance in most patients, differently from what is observed with calcium solutions at 2.5 mEq/L.[6] This positive calcium balance can determine the suppression of secretion and synthesis of PTH, contributing to a higher prevalence of dynamic bone disease in patients submitted to peritoneal dialysis.

Our hypothesis is that the decrease in the calcium concentration in the PD solutions can induce an increase in serum levels of PTH-i to the range recommended by the current guidelines.

Objectives

Our objective was to evaluate the response of serum levels of PTH in six months after the decrease in calcium concentrations of the dialysate calcium in patients undergoing PD.

Material and Methods

This was a prospective, observational study, carried out in a single Brazilian renal replacement therapy (RRT) center. The study population consisted of all prevalent patients (more than 90 days) undergoing PD selected during the period from January 2008 to January 2009 that met the following inclusion criteria: (1) age older than 18 years; (2) serum PTH < 150 pg/mL in the month of study enrollment; (3) use of PD solution with a calcium concentration of 3.5 mEq/L for at least 30 days. The exclusion criteria were: absence of a second analysis of serum PTH six months after the basal assessment. The follow-up period of the last patient ended in June 2009. All patients signed the Free and Informed Consent Form, authorizing the use of their test results for scientific purposes.

All nephrologists involved in the treatment of the study patients had the power to decide, at any moment, to convert or not their patients to calcium solutions at 2.5 mEq/L, as deemed necessary. At the end of the follow-up period, the patients were divided in two groups: a group that started and finished the treatment using a calcium solution at 3.5 mEq/L (Control) and a group that was converted to a calcium solution at 2.5 mEq/L (Intervention) during the follow-up period.

All testes were collected according to the clinic's routine and according to the norms established by Resolução da Diretoria Colegiada #154.

Statistical analysis

Continuous variables are presented as means ± SD. Categorical variables are presented as percentages. The Student's *t* test was sued to compare means between 2 distinct groups. A p value < 0.05 was considered significant. Analysis of covariance was carried out with ΔPTH as dependent variable and age and time of dialysis as co-variables.

Results

During the recruiting period, thirty-five patients met the inclusion criteria. Of these, twenty-two were converted to the calcium solution at 2.5 mEq/L and thirteen kept using the calcium solution at 3.5 mEq/L. No patients were excluded from the study. Mean age was 62 ± 17 years and diabetic nephropathy was the main underlying disease causing CKD (36%), followed by hypertensive nephrosclerosis (25%) and chronic glomerulonephritis (14%). The comparison of demographic and laboratory characteristics between the two groups is shown in Table 1.

The Control group presented a higher prevalence of diabetes as the underlying disease, when compared to the Intervention group (54% *versus* 30%, NS). However, there was no statistically significant difference between diabetic and non-diabetic patients, when compared regarding age (61.4 *versus* 61.5 years; p = 0.99), basal PTH values (79 *versus* 85pg/dL; p = 0.69), calcium (9.4 *versus* 9.8 mg/dL; p = 0.34) and phosphorus levels (4.7 *versus* 4.8mg/dL; p = 0.78).

Although PTH values increased significantly in both groups, the increase was significantly higher in the Intervention, when compared to the Control group, after six months of follow-up (ΔPTH 194 *versus* 92 pg/dL; p < 0.05) Figure 1. In the Intervention group, 41% of the patients reached PTH levels in six months that were within the target range recommended by the current guidelines (2 to 9 times the upper normality limit or 150-500 pg/dL) *versus* 14% in the Control group (p < 0.05) Figure 2. There was no significant alteration in phosphorus, calcium and alkaline phosphatase levels after the conversion to low-calcium concentration solution (Table 2).

The Control group presented a time of dialysis that was longer than the Intervention group, although there was no statistical significance (30 ± 28 *versus* 17 ± 23; p 0.12). Due to the known association between age and ABD, we divided and evaluated the patients in two groups, one younger than 65 and the other older than 65 years. There was no significant difference between these two subgroups in relation to

basal values and after six months of PTH, calcium, phosphorus and alkaline phosphatase.

The analysis of covariance using age and time of dialysis as possible confounding factors had estimated means of ΔPTH = 189 ± 44 for group with a calcium solution of 2.5 mEq/L and 94 ± 49 for the control group ($p < 0.05$).

Discussion

The calcium balance in peritoneal dialysis (PD) is closely related to the concentration of this ion in the dialysis solution.[6] A positive calcium balance can induce hypercalcemia, inhibit the secretion of PTH and stimulates the development of adynamic bone disease in patients undergoing PD.

The causes of low bone remodeling in chronic kidney disease (CKD) are multiple and among them are the low levels of 1.25 dihydroxyvitamin D, metabolic acidosis and calcium overload (as phosphorus chelating agents or offered in the dialysis bath), in addition to low levels of estrogen and progesterone, systemic inflammation and unintentional ample use of vitamin D. Three important clinical conditions associated with ABD and that are often observed in patients undergoing PD include diabetes mellitus, older age and malnutrition.[7]

The two main determinants of a positive calcium balance, in addition to its concentration in the dialysis solution, have been determined by Montenegro *et al.*, who found an important negative correlation of the calcium balance (in patients undergoing CAPD) between the total ultrafiltration values ($r = -0.7$, $p < 0.00001$) and the serum calcium concentration ($r = -0.49$, $p < 0.0001$). Although there are a few studies in which the serum PTH levels did not increase with the use of calcium solutions at 2.5 mEq/L, most of them have shown that this is a frequent response to the decrease in calcium concentrations in the dialysis bath.[8-13] Pagliari *et al.*, in the beginning of the 90s, were among the first to verify the increase in serum levels of PTHi in 10 patients undergoing CAPD 48 hours after the dialysis solution was exchanged by a calcium solution of 2.5 mEq/L.[13] Johnson *et al.* compared the clinical, biochemical and radiological parameters of 45 patients randomized to solutions with different calcium concentrations.[9] PTH levels increased

Figure 1. PTH values.

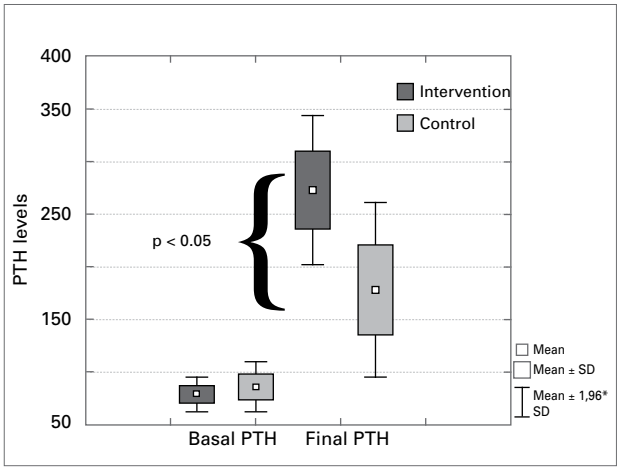

Figure 2. PTH levels in 6 months.

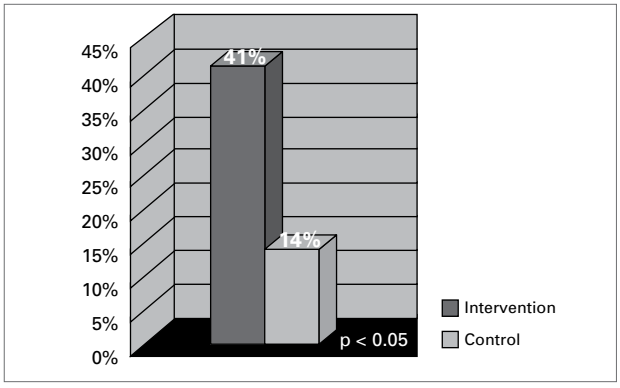

Table 1 Comparison of the variations in laboratory assessments in the groups at basal time and after six months

Variable	Group		p
	Control	Intervention	
Age	66 ± 1	60 ± 1	0.51
Female sex	38%	30%	0.62
Diabetes	54%	30%	0.16
Initial dose $CaCO^3$ (mg)	1807 ± 1601	1477 ± 1577	0.55
Time of dialysis (months)	30 ± 28	17 ± 23	0.12
Basal PTH	86 ± 44 pg/mL	79 ± 38 pg/mL	0.51
Basal calcium	9.7 ± 0.9 mg/dL	9.5 ± 0.9 mg/dL	0.85
Basal phosphorus	4,8 ± 1.5 mg/dL	4.8 ± 1.0 mg/dL	0.82
Basal alkaline phosphatase	191 ± 157 mg/dL	141 ± 70 mg/dL	0.003

t test (independent samples): $CaCO^3$ = Calcium Carbonate.

Table 2 Comparison of the variations in laboratory assessments in the groups at basal time and after six months

Variable	Time		p
	Basal	6 mounths	
PTH			
intervention	79 ± 38 pg/dL	273 ± 170 pg/dL	p < 0.001
control	86 ± 44 pg/dL	178 ± 152 pg/dL	p < 0.05
Calcium			
intervention	9.5 ± 0.9 mg/dL	9.0 ± 0.9 mg/dL	p = 0.14
control	9.7 ± 0.9 mg/dL	9.3 ± 0.6 mg/dL	p = 0.12
Phosphorus			
intervention	4.8 ± 1.0 mg/dL	5.4 ± 1.1 mg/dL	p = 0.13
control	4.8 ± 1.5 mg/dL	4.5 ± 1.2 mg/dL	p = 0.5
Alkaline phosphatase			
intervention	141 ± 70 mg/dL	123 ± 77 mg/dL	p = 0.38
control	191 ± 157 mg/dL	131 ± 92 mg/dL	p = 0.44

t test (dependent samples).

significantly in the first six months of follow-up, an increase that did not persist after one year, probably due to the use of calcium-based and calcitriol-based phosphorus chelating agents. The impact of the increase in PTH levels caused by the use of calcium solutions at 2.5 mEq/L had not been assessed until Sanchez *et al.* randomized 44 patients to a calcium solution at 2.5 mEq/L or 3.5 mEq/L and evaluated the bone histology of these individuals in the beginning of therapy and after one year of follow-up.[12] Although they found a significant increase in PTH levels in the group submitted to calcium solutions at 2.5 mEql/L after 3, 6, 9 and 12 months, there was no alteration in histological pattern between the two groups. Differently, Haris *et al.* reported the normalization of bone histology in patients with adynamic bone disease after the conversion to calcium solution at 2.5 mEq/L in 16 months.[8]

In the present study, we evaluated the impact of the use of a calcium solution at 2,5 mEq/L on PTH values in patients undergoing DP. The two groups assessed (Intervention and Control) presented a significant increase in PTH levels after six months of follow-up. The increase in the PTH values in the Intervention group was higher and more significant than in the Control group. However, there is no evidence in the literature on the risk of developing hyperparathyroidism with the chronic use of calcium solutions at 2.5 mEq/L and its use must be evaluated individually for each case.

The other biochemical parameters related to mineral metabolism (total calcium, phosphorus and alkaline phosphatase) were not different between the two groups. No patient included in the study was using or used calcitriol or vitamin D during the follow-up period. Similarly, there was no difference regarding the dose of phosphorus chelating agents used by the groups, both at the initial assessment and after the six-month study period.

Known confounding factors that can interfere with PTH values were assessed. Age, an independent risk factor for the development of ABD,[4,11,14] did not interfere with the variables of mineral metabolism in the present study. Similarly, the time of dialysis was not a factor that was significantly associated with PTH variation between the groups and in general (data not shown). Regarding the metabolism of carbohydrates, in spite of the knowledge that hyperglycemia and insulin deficiency can inhibit the secretion of PTH and that the products of advanced glucose degradation alter the responsiveness of osteoblasts to regulatory hormones and cytokines,[15] the presence of diabetes was not a determinant factor on PTH levels at basal time and after 6 months.

Among the several limitations of the present study, we can mention the fact that it was carried out in a single center; the sample size was small; the absence of serum albumin analysis in the patients, a factor recently associated with low bone remodeling;[16] the lack of measurement of patients' residual diuresis, of which presence is of utmost importance in phosphorus excretion, as well as data on ultrafiltration.

As this was not a randomized study and due to the doctors' autonomy in choosing or not the use of a calcium solution at 2.5 mEq/L, it is not possible to rule out that the conversion to this solution might have been influenced by variables that were not analyzed, such as previous hypercalcemia and difficulty to administrate chelating agents.

In conclusion, the use of a calcium solution at 2.5 mEql/L is an effective option to increase PTH levels in patients that present levels below those recommended by the guidelines in the short term. The individualization of the prescription, according to the needs and responses of each patient to the different solutions of PD remains the most sensible approach, until evidence that establishes the best approach strategy for mineral disorders in patients undergoing PD is demonstrated.

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