Long-term effects of reducing the dialysate calcium concentration on bone biomarkers in adult patients on peritoneal dialysis

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Abstract

Introduction:

Patients on peritoneal dialysis (PD) are usually exposed to a high dialysate calcium concentration (D[Ca]), which is associated with undesirable effects. Low D[Ca] might overstimulate parathyroid hormone (PTH), as shown by previous studies carried out before the incorporation of calcimimetics in clinical practice. We hypothesized that a reduction in D[Ca] is safe and without risk for a rise in serum PTH.

Methods

in this prospective study, the D[Ca] was reduced from 1.75 mmol/L to 1.25 mmol/L for one year in prevalent patients on PD. Demographic, clinical, and biochemical parameters were evaluated at baseline, 3, 6, and 12 months of follow-up.

Results

Patients (N = 20) aged 56 ± 16 years, 50% male, 25% diabetic. There was no significant change in calcium, phosphate, alkaline phosphatase, 25(OH)-vitamin D or PTH over time. Medication adjustments included an increase in calcitriol and sevelamer. After 1 year, absolute and percentual change in PTH levels were 36 (-58, 139) pg/ml, and 20% (-28, 45) respectively. The proportion of patients with PTH > 300 pg/ml did not change during the follow-up (p = 0.173).

Conclusion

Low D[Ca] concentration should be considered to patients on PD as a valuable and safe option. Medication adjustments to detain PTH rising, however, are advised.

Introduction

Mineral and bone metabolism disorder in the context of chronic kidney disease (CKD-MBD) constitutes a major complication defined as abnormalities in serum calcium, phosphorus, parathyroid hormone (PTH), and vitamin D, in association with vascular calcification. CKD-MBD contributes to the high mortality rate among patients on dialysis [1]. Calcium and phosphate metabolism disorders are common in patients on dialysis and have been associated with vascular calcification, arterial dysfunction and increased morbidity, and mortality [1–4]. A positive calcium load has a huge negative impact on vascular calcification for both PD [5] and hemodialysis patients [6]. Therefore, maintaining a neutral calcium and phosphate balance and suitable PTH levels has become the focus of attention. The dialysate calcium concentration (D[Ca]) might play a role in this management.

D[Ca] is a pivotal factor influencing serum calcium, phosphate, and PTH levels. In both continuous ambulatory PD (CAPD) and automated PD (APD), patients are continuously exposed to dialysate for several hours during

the dwelling time. Generally speaking, D[Ca] 1.75mmol/L, which is considered the standard D[Ca] in PD, may produce soft-tissue calcification and adynamic bone disease, whereas D[Ca] of 1.25 mmol/L may reduce the incidence of hypercalcemia, but stimulate PTH secretion [7]. A recent metanalysis has suggested that a 1.75 mmol/L D[Ca] should be the choice for PD patients with secondary hyperparathyroidism [8]. On the other hand, D[Ca] of 1.25 mmol/L has been recommended to stimulate PTH, reducing the risk of adynamic bone disease (ABD) [9].

However, so far, only a few trials have tested the impact of reducing the D[Ca] on bone biomarkers. In addition, there is scarce data in latest 10 years, a clinical scenario with a spread use of APD, and more availability of CKD-MBD-related medication. We hypothesized that a reduction of D[Ca] from 1.75 mmol/l to 1.25 mmol/l over a 12-month period is safe and would have no significant impairment in CKD-MBD biochemical markers including in the risk of rising PTH.

Methods

Study Design: This was a single-center interventional study, in which patients were assigned to change the D[Ca] from 1.75 mmol/L (standard-calcium) to 1.25 mmol/L (low-calcium) for one year.

Glucose concentration, inflow volume, and the number of exchanges a day were responsibilities of the physician in charge. Physicians were free to adjust the dose of dialysis and medications to maintained mineral and bone biomarkers within the recommended target.

Setting: stable adult patients on PD were recruited at the Hospital das Clinicas HCFMUSP, Universidade de Sao Paulo, Brazil, in the period between December 2017 and March 2020.

Participants: the inclusion criteria were patients > 18 years old who were on PD for at least 3 months. The exclusion criterion was severe hypocalcemia (total calcium < 7.5 mg/dl).

The local Research Ethics Board of the Hospital da Clínicas da Universidade de São Paulo (Cappesq# 30284714.0.0000.0068) has approved the study protocol. All participants provided written informed consent to participate in the study.

Variables of interest were etiology of renal disease, age, weight, blood pressure, presence of comorbidities such as hypertension and diabetes mellitus, history of coronary and cerebrovascular disease, active medications, time on PD, and type of dialysis. We also collected data on residual diuresis, renal kt/V, and body composition, assessed by electrical bioimpedance. Biochemical variables evaluated included total and ionized calcium (tCa and iCa), phosphorus (P), 25(OH)-vitamin D, PTH, alkaline phosphatase (ALP), and hemoglobin (Hb).

The outcomes evaluated were changes in PTH, tCa, iCa, P, vitamin D, and ALP levels. These markers were assessed at baseline, 3, 6, and 12 months after the intervention.

Laboratory Measurements: all biochemical analyses were done according to the manufacturer's instructions and usual techniques. Hb was measured using Laser/spectrophotometry (Reference range – RR: 13.5–17.5 g/dl for men and 12.0-15.5 g/dl for women), tCa and P were measured by colorimetric method (RR 8.4–10.2 mg/dl, and 2.7–4.5 mg/dl, respectively), iCa was measured by an ion-selective electrode (RR 4.73–5.29 mg/dl); ALP

was measured by colorimetric method (RR 35–104 U/L in women and 40–129 U/L in men); 25OH-vitamin D was measured by chemiluminescence (RR 30–100 ng/ml). PTH was measured by chemiluminescence immunoassay (RR 11–65 pg/mL; Roche immunoassay analyzer, Roche Diagnostics, Germany).

Bias: to minimize the bias, the same observer collected biochemical data e follow the medical consultations to assure adherence to the prescribed drugs.

Study size: adopting PTH levels as the main outcome, the required sample size to reach 5% of alpha error and 80% of power was calculated in 18 patients, in a repeated-measures study design.

Statistical analysis: the results are presented as the mean ± SD or median and (25, 75) quartiles depending on the normality of the data, tested by Shapiro-Wilk. General linear model (GLM) repeated measures procedure was used to test the effect of reduction in D[Ca] on variables of interest. P-value obtained described the within-subject difference (baseline, 3, 6, and 12 months). When Mauchly's test of sphericity was violated ($p < 0.05$), we used the Greenhouse-Geisser correction. The correlation coefficients were Pearson or Spearman, depending on the normality of the data. A p-value < 0.05 was considered significant.

Analyses were performed with the use of SPSS 21.0 (SPSS Inc., Chicago, Ill., USA) and GraphPad Prism® software version 7.0 (GraphPad Software, Inc., Calif., USA).

Results

Twenty patients were included, aging 56 ± 16 years, 50% men, 25% with diabetes, on PD for a median time of 7.8 months (3, 19). The mean urea renal kt/V was 1.4 ± 0.8. Most patients were on APD (95%), had residual diuresis (1,287 ± 616 ml), and only one patient was anuric. The causes of kidney disease included chronic glomerulonephritis in 65% of patients, diabetic nephropathy in 25% of patients, and hypertensive nephrosclerosis in 15% of patients. PTH at baseline was < 150 pg/ml, 150–300 pg/ml and > 300 pg/ml in 2 (10%), 7 (35%) and 11 (55%) patients, respectively. Most patients with PTH > 300 pg/ml (72.7%) were on cinacalcet or vitamin D analogs treatment at the study entry. Two patients had mild hypocalcemia (5%) and 1 patient (2.5%) had hyperphosphatemia. Despite cholecalciferol supplementation, vitamin D levels were reduced in all but 2 patients.

Table 1 shows laboratory changes during the study. There was no significant change in tCa, iCa, P, ALP, albumin, 25(OH)-vitamin D or PTH over time. There was a reduction in Hb levels in the sixth month, returning to baseline levels after 1-year of follow-up. Biochemical changes in tCa, iCa, P, hemoglobin, and AP did not reach more than 2% during the follow-up. Regarding 25(OH)vitamin D levels and PTH, we observed an increase of 14% and 20%, respectively. Patients who had a percentual increase of at least 20% in PTH did not differ for the remained sample regarding age, sex, dialysis duration, presence of diabetes, BMI, blood pressure, diuresis, or any biochemical parameter (all p values > 0.05). Figure 1A illustrated a PTH variation in 1-year and Fig. 1B shows the percentage of patients with PTH > or ≤ 300 pg/ml in the same period. Detailed individual PTH variation is shown in Supplementary Fig. 1.

Table 1
Laboratorial changes during the follow-up.

Variable	Baseline	3 mo	6 mo	12 mo	Effect of time	1 year-absolute change	1-year relative change	Maximal change Absolute/percentual
TCa, mg/dl	8.8 ± 0.4	8.9 ± 0.7	8.8 ± 0.5	8.7 ± 0.6	0.545	-0.1(-0.6, 0.3)	-1.0(-6.6, 3.7)	0.8/9.3
Corrected TCa, mg/dl	9.0 ± 0.6	9.1 ± 0.8	8.9 ± 0.6	9.1 ± 1.0	0.894	-0.1(-0.4, 0.4)	-1.1(-4.8, 5.3)	3.1/32.7
iCa, mg/dl	4.83 ± 0.31	4.81 ± 0.40	4.72 ± 0.34	4.77 ± 0.37	0.204	-0.05(-0.20, 0.08)	-1.07(-4.30, 1.54)	0.17/3.29
P, mg/dl	4.5 ± 0.7	4.9 ± 0.7	5.0 ± 0.7	4.8 ± 1.0	0.154	0.1(-0.3, 0.5)	2.0(-6.9, 15.4)	3.3/75.0
AP, U/L	90 ± 49	91 ± 44	87 ± 41	92 ± 47	0.162	0(-9.2, 20.2)	0.2(-14.7, 26.6)	113.0/117.7
25Vit.D, ng/mL	25.5 ± 7.7	30.1 ± 8.7	31.4 ± 10.0	29.3 ± 7.7	0.061	7.8 (3.0, 19.1)	14.3(-4.8, 40.3)	15.2/113.3
PTH, pg/mL	341 ± 173	347 ± 165	376 ± 170	381 ± 189	0.675	36(-58, 139)	20(-28, 45)	383.0/113.3
Hb, g/dl	12.0 ± 1.9	11.7 ± 1.4	11.1 ± 1.6#	11.3 ± 2.0	**0.020**	-0.2(-1.9, 0.4)	-1.8(-16.6, 2.7)	2.1/20.0

Mo, months; TCa, total calcium; iCa, ionized calcium; P, phosphate; AP, alkaline phosphatase; 25Vit.d, 25(OH) vitamin D; PTH, parathyroid hormone; Hb, hemoglobin. Values expressed as mean ± SD or median (25, 75). Greenhouse-Geisser was applied for iCa and P analyses; # $p < 0.05$ vs. baseline

Table 2 shows the adjustments in medications during the study, including an increase in calcitriol and sevelamer use.

Table 2
Mineral and bone metabolism-related medications: changes during the study

Medication	Baseline	3 mo	6 mo	12 mo	P
ESA:	9 (45)	6 (30)	6 (30)	4 (20)	0.063
Don't use	11 (55)	14 (70)	14 (70)	16 (80)	
Use					
Calcitriol:	10 (50)	6 (30)	6 (30)	4 (20)	**0.023**
Don't use	10 (50)	14 (70)#	14 (70)#	16 (80)#	
Use					
Colecalciferol:	2 (10)	6 (30)	6 (30)	4 (20)	0.221
Don't use	18 (90)	14 (70)	14 (70)	16 (80)	
Use					
Cinacalcet:	16 (80)	17 (85)	17 (85)	16 (80)	0.572
Don't use	4 (20)	3 (15)	3 (15)	4 (20)	
Use					
CaCo3:	19 (95)	19 (95)	19 (95)	20 (100)	1
Don't use	1 (5)	1 (5)	1 (5)	0	
Use					
Sevelamer:	7 (35)	5 (25)	5 (25)	1 (5)	**0.005**
Don't use	13 (65)	15 (75)	15 (75)	19 (95)*	
Use					
Furosemide:	8 (40)	10 (50)	11 (55)	10 (50)	0.284
Don't use	12 (60)	10 (50)	9 (45)	10 (50)	
Use					

# $p < 0.05$ *vs.* baseline

Discussion

Clinical guidelines emphasize the importance of individualization of CKD-MBD treatment, translating best evidence into best practice. However, the guidelines revealed the lack of a high level of evidence to support the recommendations while treating patients on PD since most studies were done in a hemodialysis scenario [10].

We have demonstrated that reducing the dialysate calcium content from 1.75 to 1.25 mmol/L was safe, although had caused an increase in PTH levels requiring an adjustment in CKD-MBD-related medications. The findings from our study shed light on the new era literature, by demonstrating that calcimimetics and vitamin D analogs are capable to maintain PTH levels within recommended values even when the calcium dialysate is low.

Although we have included a relatively small number of patients, our sample characteristics reflect the Brazilian population, according to the BRAZPD cohort, that has included 9,905 patients, age 58.9 ± 16 years, 48% men. In Brazil, the use of APD substantially increased from 37–53%, in 5 years [11], and, likewise in the current study, 95% of patients were on APD. The prevalence of diabetic patients, however, was lower in our study (25% vs. 43% in the BRAZPD data).

ABD seems to be more frequent among patients in PD [7, 12]. A previous study from our group has demonstrated that half of the patients on PD presented ABD, in a sample characterized by a high prevalence of diabetes [13]. Bone biopsy studies in PD patients who underwent a reduction in the D[Ca] revealed no change in the histological pattern [14]. Unfortunately, we have no bone biopsy data to make a fair comparison with previous results. Yet, most of our patients had secondary hyperparathyroidism, and ABD is unlikely to occur in this scenario. Of note, we have not included cases of severe secondary hyperparathyroidism (PTH > 800 pg/ml).

A previous study that has evaluated bone histomorphometry parameters has revealed that low D[Ca] improved ABD only in 4 out of 10 patients in 1 year. In addition, the authors observed that serum Ca, P and bone histological outcomes did not differ between low and high D[Ca] [14]. In 2006, a study has found a rise in PTH levels by 300% associated with an increase in bone formation rate, and a reduction of hypercalcemia after reducing the D[Ca] [9] in 14. Of note, the mentioned study reduced the D[Ca] to 1.0 mmol/L, a solution not usually commercially available, and patients were followed for a longer period than were in the present study.

Our results showed that the increase in PTH levels caused by a low D[Ca] could be managed with an adjustment in calcitriol and sevelamer use. The literature has shown an increase in PTH levels by reducing the D[Ca], since the early 1990s [15], a result confirmed by others [16]. Hutchinson et al. [17], however, have found a decrease in PTH levels after six months of treatment with 1.25 mmol/L D[Ca], although patients were receiving high doses of oral calcium carbonate. Bro et al. [18] have reviewed 24 studies covering the use of different D[Ca] in CAPD patients and found that, after treatment with 1.25 mmol/L D[Ca], patients with elevated PTH levels were at greater risk of secondary hyperparathyroidism. At that time, non-calcium-containing phosphate binders and cinacalcet were not yet available.

To our knowledge this is the first study that has included most participants on APD, showing that the 1.25 mmol/L D[Ca] did not cause a significant PTH rising since the medication is adjusted. Despite these strengths, the results of our study need to be interpreted considering its limitations. There was only a single center PD involved, the continuity effect between interventions could not be completely ruled out, there was no patient with severe hyperparathyroidism (considering PTH > 800 pg/ml), the prevalence of diabetes was low, and calcium balance was not evaluated.

In view of our results, we believe that a 1.25 mmol/L D[Ca] can be safely used in PD patients who comply with their MBD treatment. However, the optimal calcium concentration in PD solution is still uncertain and the 1.25

mmol/L D[Ca] should be individualized, with no solution called as standard.

Declarations

Author contributions: RME conceived and designed the study. MCTP, LC, and EAG conducted the study and contributed to data acquisition. RME performed statistical analysis. MCTP, RMAM and RME, performed the manuscript drafting. HA, BJP, VJ, RMAM and RME, contributed to important intellectual content during manuscript drafting. Each author was involved in the approval of the final version of the manuscript.

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Availability of materials and data: data is available to authors upon reasonable request.

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Figures

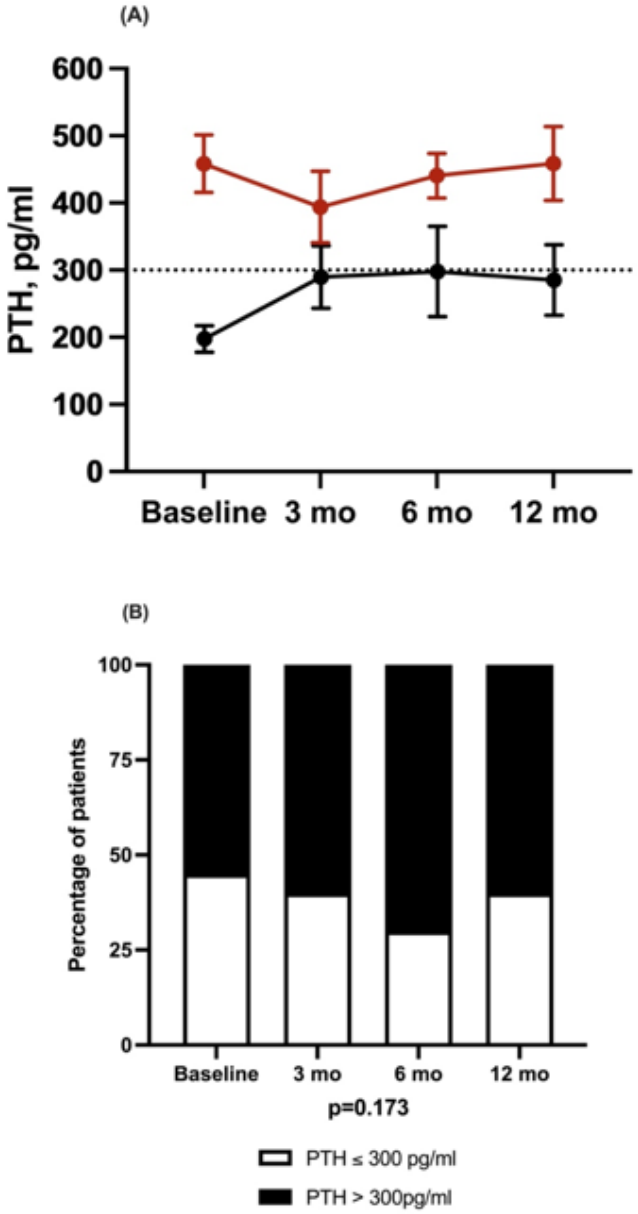

Figure 1

Changes in PTH levels (Figure 1A) and in the percentage of patients with PTH > or ≤ 300 pg/ml in 1-year of observation (Figure 1B).

Supplementary Files

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- SupplemFig1.jpg