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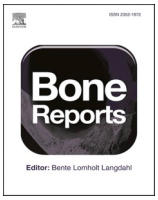

A feasibility study of avoiding positive calcium balance and parathyroid hormone increase in patients on peritoneal dialysis

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ABSTRACT

Background: The effect of the dialysate calcium concentration (D[Ca]) on mineral and bone metabolism in patients on peritoneal dialysis (PD) is overlooked. D[Ca] of 1.75 mmol/L is still prescribed to many patients on PD around the world. Previous studies on the effects of reducing D[Ca] have been carried out before the incorporation of calcimimetics in clinical practice. We hypothesized that a reduction in D[Ca] is safe and without the risk of a rise in serum parathyroid hormone (PTH).

Methods: In this non-randomized clinical trial, 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 CKD-MBD-related biomarkers were evaluated at baseline, 3, 6, and 12 months of follow-up.

Results: 20 patients completed 1-year follow-up (56 ± 16 years, 50 % male, 25 % diabetic, 55 % with baseline parathyroid hormone – PTH >300 pg/mL). Over time, there was no significant change in calcium, phosphate, total alkaline phosphatase, 25(OH)-vitamin D or PTH, although adjustments in calcitriol and sevelamer prescription were required. 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: Knowing the risk of a positive calcium balance in patients on PD, reducing the D[Ca] concentration is a safe and valuable option, although medication adjustments are needed to detain PTH rising.

1. Introduction

Mineral and bone metabolism disrorder 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 and bone anomalies. CKD-MBD contributes to the high mortality rate among patients on dialysis (Block et al., 2004). Calcium and phosphate metabolism disorders are common in patients on dialysis and have been associated with myocardial hypertrophy, vascular calcification, arterial dysfunction and increased morbidity and mortality (Block et al., 2004; Goodman et al., 2000; Qunibi et al., 2002; London et al., 2007). A positive calcium load has a huge negative impact on vascular calcification for both PD (Liang et al., 2014) and hemodialysis patients (Chertow et al., 2004). Therefore, maintaining neutral calcium and phosphate balance and suitable PTH levels has become the focus of attention.

Patients on PD are continuously exposed to dialysate for several hours during dwelling time. Although guidelines recommend a dialysate calcium concentration (D[Ca]) between 1.25 and 1.50 mmol/L (C.K.D.M.B.D.U.W.G, 2011; Uhlig et al., 2010), a D[Ca] of 1.75 mmol/L is still prescribed to up a large proportion of patients on PD around the world, reaching 50 % of those in the USA (Wang et al., 2020). Whereas D[Ca] of 1.75 mmol/L produces soft-tissue calcification and adynamic bone disease, D[Ca] of 1.25 mmol/L stimulates PTH secretion (C.K.D.M.B.D.W.G, 2009), and therefore, has been recommended to reduce the risk of

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adynamic bone disease (Haris et al., 2006).

So far, only a few trials have tested the impact of reducing the D[Ca] on bone biomarkers (Cao et al., 2015; Jin et al., 2019; Moraes et al., 2010; Demirci et al., 2009). In addition, there is scarce data in latest 10 years, a clinical scenario with a spread use of automated peritoneal dialysis (APD), and more availability of CKD-MBD-related medication. We challenged the suggestion that a 1.75 mmol/L D[Ca] should be the choice for PD patients with secondary hyperparathyroidism (Jin et al., 2019) and 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.

2. Materials and methods

This was a single center planned not randomized interventional clinical trial, in which patients were assigned to change the D[Ca] from 1.75 mmol/L to 1.25 mmol/L for one year. All patients on maintenance PD at the time of study initiation were invited. Out of 43 patients, 34 fulfilled the inclusion criteria and were invited to participate. One patient refused to participate, and 1 patient was submitted to kidney transplant before the dialysate change. Out of 30 patients, 12 patients switched to hemodialysis (3 due to peritonitis and 9 for technique failure). A final sample of 20 patients completed the 1-year follow-up, as detailed in the flowchart (Supplementary Fig. 1). Physicians were free to adjust the dose of dialysis, glucose concentration, inflow volume, number of exchanges and CKD-MBD-related medications.

Setting & participants: 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. The inclusion criteria were patients >18 years old who were on PD for at least 3 months.

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 on July 6th, 2017. All participants provided written informed consent to participate in the study. We followed the procedures in accordance with the Helsinki Declaration.

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 dialysis modality (APD vs. continuous ambulatory peritoneal dialysis – CAPD). 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), phosphate (P), 25(OH)-vitamin D, PTH, total 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 4.49–5.29 mg/dL); Hypocalcemia was defined as total serum calcium below 8.4 mg/dL or ionized calcium below 4.49 mg/dL. Hyperphosphatemia was defined as serum P > 4.5 mg/dL. Total AP 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). Any prescribed amount of cholecalciferol to achieve a minimal of 30 ng/mL of 25OH-vitamin D was considered a supplementation. PTH was measured by chemiluminescence immunoassay (RR 11–65 pg/mL; Roche immunoassay analyzer, Roche Diagnostics, Germany).

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

Study size: a convenience sample of at least 20 patients was considered.

2.1. 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 Anderson-darling test. 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 ($p < 0.05$), degrees of freedom were corrected using 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 26.0 (SPSS Inc., Chicago, Ill., USA) and GraphPad Prism® software version 8.0 (GraphPad Software, Inc., Calif., USA).

3. Results

Characteristics of patients are described in Table 1. 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. According to KDIGO guidelines (C.K.D.M.B.D.U.W.G, 2011), 1 patient (5 %) had PTH < 2× ULN (<130 pg/mL), 16 patients (80 %) had PTH between 2-9× ULN (PTH between 131 and 585 pg/mL) and 3 patients (15 %) had PTH > 9× ULN (PTH > 585 pg/mL). At baseline, 2 patients had mild hypocalcemia (5 %) and 1 patient (2.5 %) had hyperphosphatemia. Despite cholecalciferol supplementation, vitamin D levels were <30 ng/mL in all but 2 patients.

Table 2 shows laboratory changes during the study. Over time, there was no significant change in tCa, iCa, P, AP, albumin, 25(OH)-vitamin D or PTH. Changes in tCa, iCa, P, and AP did not reach >2 % during the follow-up. We observed an increase in 25(OH)vitamin D and PTH levels by 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). Fig. 1A illustrated a PTH variation in 1-year follow-up 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. 2.

Table 3 shows the adjustments in medications during the study, including an increase in calcitriol and sevelamer use, as well as an increase in their dosage.

Table 1
Characteristics of patients.

Parameter	N = 20
Age, years	56 ± 16
Male gender, n (%)	10 (50)
Non-white, n (%)	2 (10)
Cause of chronic kidney disease, n (%)	
Hypertension	3 (15)
Diabetes	5 (25)
Glomerulonephritis	12 (60)
Dialysis duration, months	7.8 (3, 19)
Urea Kt/V	1.4 ± 0.8
Automatic peritoneal dialysis, n (%)	19 (95)
Residual diuresis, mL	1287 ± 616

Values are expressed as mean ± SD, median (25,75) or percentage.

Table 2
Laboratorial changes during the follow-up.

Variable	Baseline	3 mo	6 mo	12 mo	Effect of time	1 year-absolute change
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)
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)
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)
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)
AP, U/L	76 (56, 100)	79 (58, 123)	75 (63, 106)	78 (61, 97)	0.937	0(−9.2, 20.2)
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)
PTH, pg/mL	341 ± 173	347 ± 165	376 ± 170	381 ± 189	0.675	36(−58, 139)

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

4. 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 (C.K.D.M.B.D.U.W.G, 2011). We have demonstrated that reducing the dialysate calcium content from 1.75 to 1.25 mmol/L was safe, although was associated with 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. This is an encouraging approach knowing that a positive calcium balance should be avoided in these patients.

Although we have included a relatively small number of patients, our sample characteristics reflect the Brazilian population, according to the BRAZPD cohort, which has included 9905 patients aging 58.9 ± 16 years old (48 % men). The prevalence of diabetic patients, however, was lower in our study (25 % vs. 43 % in the BRAZPD data). Most of our patients were on APD, a modality that has considerably increased over the past years in Brazil (de Moraes et al., 2014) and worldwide (Moist et al., 2014; Kramer et al., 2018; US Renal Data System, 2017). Indeed, in the United States of America, PD is almost synonymous of APD (Saran et al., 2015) and has been applied to >90 % of patients on PD. Vitamin D levels did not increase over time despite oral supplementation. This finding might be associated to the loss of vitamin D through the PD fluid, as previously described (Shany et al., 1984; Sahin et al., 2009), although this is merely speculative.

The adynamic bone disease seems to be more frequent among patients on PD (C.K.D.M.B.D.W.G, 2009; Coen, 2005). A previous study from our group has demonstrated that half of the patients on PD presented adynamic bone disease, in a sample characterized by a high prevalence of diabetes, low percentage of automatic PD, and none of patients on cinacalcet therapy (de Oliveira et al., 2015). Carmen Sánchez M. et al. found ABD in 63.2 % of patients on PD., a population characterized by higher age, diabetes, calcium salt intake, calcitriol doses and lower PTH levels (Carmen Sanchez et al., 2000). In the current study, only 10 % of patients had PTH levels <150 pg/mL at baseline.

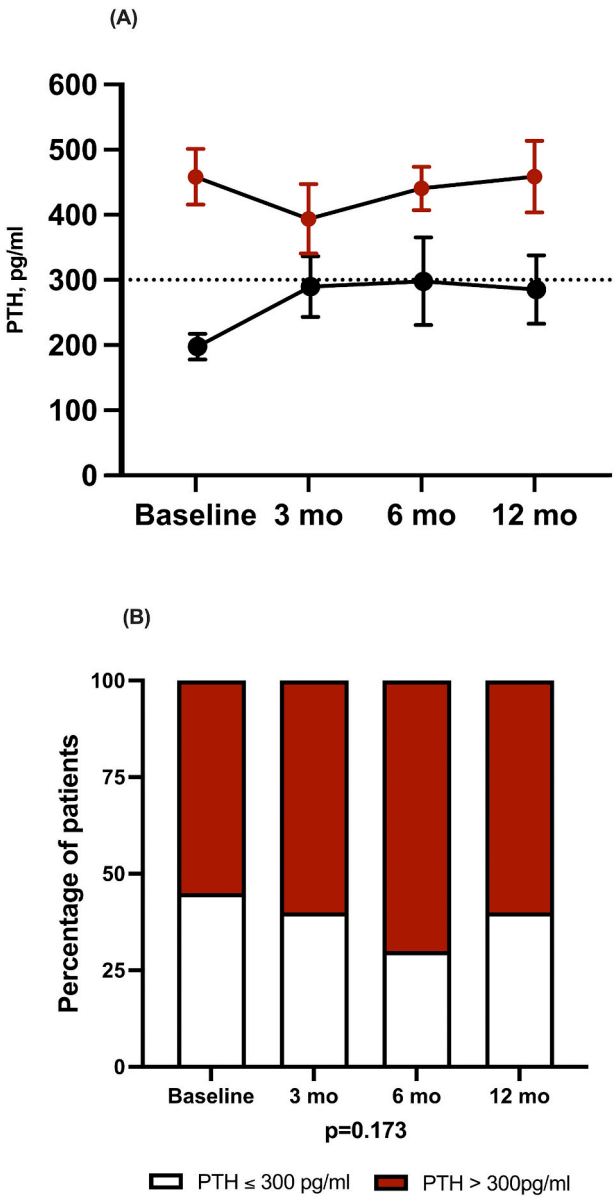

Fig. 1. A. Changes in parathyroid hormone (PTH) during the study period. Symbols and lines represent mean and standard error of the mean according to PTH at baseline >300 pg/mL (red) or ≤300 pg/mL (black).
B. Percentage of patients with parathyroid hormone (PTH) > 300 pg/mL (filled red columns) or ≤300 pg/mL (empty white columns).

However, PTH levels higher than 150 pg/mL, as an isolate parameter, do not exclude the presence of ABD. Indeed, we found that 49 % of patients had ABD. Patients with diabetes are more likely to suffer from ABD, which is characterized by a low bone capacity to incorporate calcium and inability to handle an extra calcium load, potentially accelerating vascular calcification (Frazao and Martins, 2009). Previous study from our group also demonstrated an association between ABD and vascular calcification (de Oliveira et al., 2015).

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 in a sample of 14 patients, in whom the D[Ca] was reduced to 1.0 mmol/L (Haris et al., 2006). Our results showed that the increase in PTH levels associated with a D[Ca] of 1.25 mmol/L could be managed with an adjustment in calcitriol and sevelamer. The availability of calcimimetics might also have contributed to our success. Cinacalcet was added to therapy in patients who developed hyperphosphatemia, allowing the

Table 3
Mineral and bone metabolism-related medications: changes during the study.

Medication	Baseline	3 mo	6 mo	12 mo	P
Calcitriol					
Don't use	10 (50)	6 (30)	6 (30)	4 (20)	**0.023**
Use	10 (50)	14 (70)#	14 (70)#	16 (80)#	
Prescribed dose mcg/ week	0.37 (0, 1.5)	1.5 (0, 2.25)	1.5 (0, 2.25)	2.25 (0.94, 2.8)	0.002
Cholecalciferol					
Don't use	2 (10)	6 (30)	6 (30)	4 (20)	0.221
Use	18 (90)	14 (70)	14 (70)	16 (80)	
Prescribed dose, UI/day	12,500 (5313-22,500)	8500 (0–12,500)	11,250 (1250-12,500)	10,000 (5000-13,625)	0.114
Cinacalcet					
Don't use	16 (80)	17 (85)	17 (85)	16 (80)	0.572
Use	4 (20)	3 (15)	3 (15)	4 (20)	
Prescribed dose, mg/day	0 (0,0)	0 (0,0)	0 (0,30)	0 (0,30)	0.486
CaCo3					
Don't use	19 (95)	19 (95)	19 (95)	20 (100)	1
Use	1 (5)	1 (5)	1 (5)	0	
Prescribed dose, mg/day	0 (0,0)	0 (0,0)	0 (0,0)	0.37 (0, 1.5)	0.261
Sevelamer					
Don't use	7 (35)	5 (25)	5 (25)	1 (5)	**0.0002**
Use	13 (65)	15 (75)	15 (75)	19 (95)*	
Prescribed dose, mg/day	1600 (400–2400)	1600 (400–2400)	2400 (1600-4800)	4000 (1800-4800)	0.021

# $p < 0.05$ vs. baseline.

continuous treatment of hyperparathyroidism. Previous studies have shown an increase in PTH levels by reducing the D[Ca], since the early 1990s (Pagliari et al., 1991), a result confirmed by others (Moraes et al., 2010). Bro et al. (1997) have reviewed 24 studies covering the use of different D[Ca] in patients on CAPD and found that, after treatment with 1.25 mmol/L D[Ca], patients with elevated PTH levels were at greater risk of secondary hyperparathyroidism. In opposite to these results, Hutchinson et al. (1992) have found a decrease in PTH levels after six months of treatment with 1.25 mmol/L D[Ca], in a sample of patients receiving high doses of oral calcium carbonate. Our study differs from previous since non-calcium-containing phosphate binders and cinacalcet are available. In addition, most patients were on CAPD, contrasting with the spread use of APD over the last years.

Data from the Dialysis Practice Patterns and Results Study (DOPPS) show there is still a considerable percentage of patients on PD receiving dialysis with d[Ca] of 1.75 mmol/L (Wang et al., 2019), which is also true for Brazil (Weissheimer et al., 2021), despite the recommendation of a d[Ca] between 1.25 and 1.50 mmol/L (Uhlig et al., 2010; C.K.D.M.B.D.W.G, 2009). Knowing the risks of a positive calcium balance for patients with advanced CKD (Elias et al., 2021), the results from our study should encourage a spread use of recommended d[Ca] from 1.25 to 1.5 mEq/L.

The strengths of our studies are: 1. the inclusion of most participants in APD, a scarcely represented modality in previous studies; 2. the longitudinal follow-up of 1 year; 3. it was a study conducted after calcimimetics had been incorporated into the clinical practice. Despite these strengths, the results of our study need to be interpreted considering its limitations. There was only a single center involved, with small sample size without a control group and with no positive control intervention. In addition, 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 relatively low, and the calcium balance was not evaluated. We analyzed biochemical biomarkers and have no data on bone biopsy and vascular calcification. In this regard, Demerci et al. (2009) have shown an association between Ca exposure through PD fluid and arterial stiffness.

We demonstrated that reducing the D[Ca] to 1.25 mmol/L was not associated with an increase in PTH levels as long as the MBD-related medications are adjusted. Knowing the adverse effects of vascular calcium calcification caused by a positive calcium balance, we strongly recommend a reduction of the D[Ca] for patients on PD, including those with high PTH levels, albeit attention is advised to adjust in MBD-related medications.

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Ethical approval

The Local Institution Review Board at the Hospital das Clinicas da Universidade de São Paulo (Cappesq# 30284714.0.0000.0068) has approved the study protocol. Written informed consent for participation was obtained from each participant. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

CRediT authorship contribution statement

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.

Declaration of competing interest

The author(s) declare no competing interests.

Data availability

Data will be made available on request.

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