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

Maria Clara Teixeira Piraciaba, Lilian Cordeiro, Erica Adelina Guimarães, Hugo Abensur, Benedito Jorge Pereira, Vanda Jorgetti, Rosa Maria Afnson Moysés, Rosilene Motta Elias

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 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 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...

* Corresponding author at: Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Serviço de Nefrologia, Rua Dr. Enéas de Carvalho Aguiar 255, 7º andar, São Paulo CEP 05403-000, SP, Brazil.

E-mail address: rosilenemotta@hotmail.com (R.M. Elias).

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ionized calcium (tCa and iCa), phosphate (P), 25(OH)-vitamin D, PTH, residual diuresis, renal kt/V, and body composition, assessed by elec
trilic bioimpedance. Biochemical variables evaluated included total and
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 ac-
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 hypocalemia (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. 1.

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 hypocalemia (5 %) and 1 patient (2.5 %) had hyperphosphatemia. Despite cholecalciferol supplementation, vitamin D levels were <30 ng/mL in all but 2 patients.

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study, only 10% of patients had PTH levels in the range of 300 pg/mL (empty white columns). 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 Sánchez et al., 2006). In the current study, only 10% of patients had PTH levels <150 pg/mL at baseline. 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

| 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 ± 0.05 | 0.34 ± 0.03 |
| Corrected TCa, mg/ | 9.0 ± 0.6 | 9.1 ± 0.8 | 9.9 ± 0.6 | 9.1 ± 0.8 | 0.989 ± 0.02 | 0.48 ± 0.04 |
| dl                |          |      |      |       |                |                        |
| iCa, mg/dL        | 4.83 ± 0.31 | 4.81 ± 0.40 | 4.72 ± 0.34 | 4.77 ± 0.37 | 0.204 ± 0.04 | 0.07 ± 0.02 |
| P, mg/dL          | 4.5 ± 0.7 | 4.9 ± 0.7 | 7.5 ± 1.0 | 4.8 ± 1.0 | 0.154 ± 0.05 | 0.26 ± 0.02 |
| AP, U/L           | 76 (58, 100) | 79 (63, 123) | 75 (61, 106) | 78 (66, 97) | 0.937 ± 0.04 | 0.20 ± 0.02 |
| 25Vit.D, ng/     | 25.5 ± 7.7 | 30.1 ± 8.7 | 31.4 ± 10.0 | 29.3 ± 7.7 | 0.061 ± 0.03 | 0.39 ± 0.02 |
| ml                | 341 ± 133 | 347 ± 165 | 376 ± 170 | 381 ± 189 | 0.675 ± 0.06 | 0.36 ± 0.03 |
| PTH, pg/mL        | 173 ± 376 | 189 ± 381 | 189 ± 381 | 189 ± 381 | 0.675 ± 0.06 | 0.36 ± 0.03 |

Mo, months; TCa, total calcium; iCa, ionized calcium; P, phosphate; AP, alkaline phosphatase; 25 Vit.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.
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 1.25 mmol/L D[Ca], patients with elevated PTH levels were at greater risk of secondary hyperparathyroidism. In opposition 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 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., 2016; 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 mmol/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 calcium kinetics 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, Demerici 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.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2022.101625.

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Ethical approval

The Local Institution Review Board at the Hospital das Clínicas 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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### Table 3

| 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 | 0.37 (0, 1.5) | 1.5 (0) | 1.5 (0) | 2.25 | 0.002 |
| dose mcg/week | 2.25 | 2.25 | (0.94) | 2.48 |
| Cholcalcoler |        |      |      |       |   |
| Don’t use  | 2 (10)   | 6 (30)| 6 (30)| 4 (20) | 0.221 |
| Use        | 18 (90)  | 14 (70) | 14 (70) | 16 (80) |   |
| Prescribed | 12,500   | 8500 | 11,250 | 10,000 | 0.114 |
| dose, UI/day | (5313-22,500) | (12,500) | (12,500) | 13,625 |   |
| Cinacalcet |          |      |      |       |   |
| Don’t use  | 16 (80)  | 17 (85)| 17 (85) | 16 (80) | 0.572 |
| Use        | 4 (20)   | 3 (15)| 3 (15) | 4 (20) |   |
| Prescribed | 0 (0.0)  | 0 (0.0) | 0 (0.30) | 0 (0.30) | 0.486 |
| dose, mg/day |      |      |      |       |   |
| CaCo3      |          |      |      |       |   |
| Don’t use  | 19 (95)  | 19 (95)| 19 (95) | 20 (100) | 1 |
| Use        | 1 (5)    | 1 (5) | 1 (5) | 1 (5) | 0 |
| Prescribed | 0 (0.0)  | 0 (0.0) | 0 (0.0) | 0.37 (0) | 0.261 |
| dose, mg/day |      |      |      |       | 1.5 |
| Sevelamer  |          |      |      |       |   |
| Don’t use  | 7 (35)   | 5 (25)| 5 (25) | 1 (5) | 0.0002 |
| Use        | 13 (65)  | 15 (75)| 15 (75) | 19 (95)* |   |
| Prescribed | 1600     | 1600 | 2400 | 4000 | 0.021 |
| dose, mg/day | (400-2400) | (400-2400) | (1600-4800) | (1800-4800) |   |

* p < 0.05 vs. baseline.

# Data availability

Data will be made available on request.
