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Case Series

Bone Mineral Parameters in Peritoneal Dialysis Patients after Lowering Calcium Concentration in Dialysis Fluids: A Case Series in Patients Using Icodextrin

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Peritoneal dialysis · Calcium · Icodextrin · Physioneal · Mineral bone disease · Phosphate binders

Abstract
In patients treated with peritoneal dialysis (PD), lowering the calcium level in PD fluids results in lower serum calcium levels and higher parathyroid hormone (PTH) levels. It is hypothesized that this effect is attenuated when patients are using icodextrin 7.5% for the once-daily long dwell (containing high calcium concentration). In this case series, we included 8 stable PD patients (mean age 68 ± 13 years, 7 male), all using icodextrin 7.5% (containing 1.75 mmol/L calcium) for the once-daily long dwell. The calcium content of the PD fluids for the remaining dwells was lowered from 1.75 mmol/L to 1.25 mmol/L. Bone mineral parameters and phosphate prescription at baseline, 6 weeks after this change, and after 6 months were compared. After lowering calcium concentration of the PD fluids – except for the icodextrin 7.5% – from 1.75 mmol/L to 1.25 mmol/L, calcium levels changed from 2.32 ± 0.11 to 2.29 ± 0.12 (p = NS); intact PTH (iPTH) from 39.6 ± 28.3 to 64.9 ± 34.5 pmol/L (p = 0.045); and alkaline phosphatase from 104.13 ± 48.75 to 101.38 ± 32.39 (p = NS). After 6 months, all bone mineral parameters were similar to baseline levels; however, slightly higher calcium-based phosphate binders were prescribed. Lowering calcium content from 1.75 mmol/L to 1.25 mmol/L in PD fluids in patients on icodextrin resulted in stable calcium values, a temporal increase in iPTH and a modest

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increase in calcium-based phosphate binder prescription. Using icodextrin for the long once-daily dwell appears to attenuate the effects on bone mineral parameters when lowering the calcium concentration of the short dwells.

Introduction

The prevalence of mineral bone disease (MBD) in patients with chronic kidney disease (CKD) is high. MBD leads to a variety of bone diseases, due to either increased or decreased bone turnover [1]. CKD-MBD is associated with vascular complications including valvular calcifications and cardiovascular death [2–6]. A disturbance in the calcium balance is one of the main drivers of MBD and adverse outcome. There is substantial evidence that hypercalcemia is associated with increased mortality in patients with CKD [7–13]. Particularly in hemodialysis patients, it has been shown that high dialyzate calcium levels (i.e., 1.75 mmol/L) are associated with adverse outcomes. Hence, dialyzate calcium levels between 1.25 and 1.5 mmol/L are recommended in these patients [14, 15]. In peritoneal dialysis (PD) patients, however, there are only limited data available on the relation between calcium levels in PD fluids and outcome [16, 17]. Hence, there are no specific recommendations for PD patients in the current KDIGO Clinical Practice Guidelines [18]. Individualized care regarding calcium content in PD fluids and phosphate binder prescription is recommended, targeted at lowering high serum phosphate and maintaining normal serum calcium.

A normal calcium balance in these patients is – among other factors – determined by the calcium content of PD fluids, calcium intake (dietary intake as well as calcium-containing medication) as well as by ultrafiltration volume. Lowering the calcium concentration in PD fluids may lead to a negative calcium balance, resulting in increasing intact parathyroid hormone (iPTH) and alkaline phosphatase (AF) levels, suggestive for high bone turnover. Subsequently, in PD patients treated with low calcium PD fluids, higher doses of calcium-based phosphate binders may be required in order to prevent secondary hyperparathyroidism [19, 20].

Short-term studies have investigated the effects of low versus high calcium concentration in PD fluids on bone mineral parameters [17, 21]. As far as we know, none of these studies have addressed a possible effect of icodextrin 7.5% (containing high calcium, i.e., 1.75 mmol/L) on the calcium balance. It can be hypothesized, however, that the use of icodextrin 7.5% for the once-daily long dwell attenuates changes in bone mineral parameters as previously observed when the calcium concentration in PD fluids was lowered.

In this case series, we report changes in bone mineral parameters and phosphate binder prescription in PD patients after switch from high (1.75 mmol/L) to low (1.25 mmol/L) calcium concentration for the short dwells while maintaining icodextrin 7.5% for the once-daily long dwell.

Case Series

As of January 2020, all Baxter Physioneal 35 PD fluids (containing 1.75 mmol/L calcium) were no longer available in the Netherlands. As a result, standard of care in our center (Northwest Clinics, Alkmaar, The Netherlands) was changed. All Physioneal 35 PD fluids (containing 1.75 mmol/L calcium) were replaced by Physioneal 40 (containing 1.25 mmol/L

calcium). The use of extraneal (icodextrin 7.5%) was unchanged. At the time of this change, we selected 10 stable PD patients, all using icodextrin 7.5% for the once-daily long dwell. The included patients visited our dialysis center every 6 weeks and underwent routine biochemical measurements, according to standard care. Two patients were lost to follow-up (1 patient received a kidney transplant and 1 patient was transferred to hemodialysis). The data from the remaining 8 patients were used for this study.

We collected data at three timepoints: (1) most recent laboratory values (3 ± 8 weeks) before PD fluid switch (Tbaseline), (2) first routine visit (6 ± 6 weeks) after PD fluid switch (Tpost), and (3) 6 months (24 ± 9 weeks) after PD fluid switch (T6months). Patient characteristics were described at baseline (Tbaseline). Medication was prescribed at the discretion of the treating nephrologist. The outcome parameters of this study were changes in the bone mineral parameters, i.e., serum calcium, phosphate, iPTH, and AF. In addition, changes in phosphate binder prescription were analyzed, subdivided in calcium-free and calcium-based binders.

To compare the laboratory values on the three timepoints, we performed univariate repeated measures ANOVA for the normally distributed continuous variables. To analyze differences in prescribed medication between the three timepoints, Friedman test, repeated measure ANOVA, or Cochran's Q test were used as appropriate. For the ordinal variables, we used Friedman test, followed by post hoc analysis with Wilcoxon's signed-rank test if significant, and Cochran's Q test if response was binary. All statistical analyses were performed with SPSS software, version 22.0 for Windows (IBM, Armonk, NY, USA) and GraphPad Prism 6 for Windows (GraphPad, San Diego, CA, USA). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534476).

The baseline characteristics of the 8 included patients are presented in Table 1. Patients were predominantly white male with mean age 68.4 ± 12.9 years. No adverse or unanticipated events were observed after switch to PD fluids with lower calcium concentrations. At baseline, bone mineral parameters were within treatment targets with mean calcium 2.32 ± 0.11 mmol/L, phosphate 1.36 ± 0.23 mmol/L, iPTH 39.6 ± 28.3 pmol/L, and AF 104 ± 49 U/L. Five patients used phosphate binders, and four of them used calcium-based phosphate binders. No patients used cinacalcet before PD fluid switch. All patients used vitamin D analogs. Bone mineral parameters over time are presented in Figure 1. As presented in Table 2, serum calcium and AF values did not change over time. Serum phosphate concentrations showed a significant mean difference between Tbaseline and Tpost (−0.262 [−0.439 to −0.086], $p = 0.007$), and iPTH concentrations showed a significant mean difference between Tbaseline and Tpost (−25.212 [−49.78 to −0.646]), $p = 0.045$). As shown in Table 3, there was a significant difference in total phosphate binder use ($\chi^2 = 6.87$, $p = 0.032$). There was also a significant difference in calcium-based phosphate binder use ($\chi^2 = 11.20$, $p = 0.004$).

Discussion

In this case series, no changes in serum calcium levels were observed in PD patients that were switched from PD fluids with high calcium to low calcium while maintaining on icodextrin 7.5% for the long once-daily dwell. However, iPTH levels did increase 6 weeks after this switch but returned to baseline values after 6 months. After 6 months, slightly more calcium-based phosphate binders were prescribed.

Several other studies have investigated the role of calcium concentration in PD dialyzate fluids. In 2019, Jin et al. [19] published a meta-analysis of these studies, also performing

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Table 1. Baseline characteristics

	Total population (*N* = 8)
Sex (*N* males)	7
Age, years	68.4±12.9
Race (*N* white)	7
Residual kidney function eGFR, mL/min	3.86±3.19
Residual urinary output, mL	916±833
Time on PD therapy, months	14.5 [11.3–30.5]
Exchange volume, mL/24 h	9,877±2,064
APD, %	75
CAPD, %	25

Presented as mean±SD or median [interquartile range].

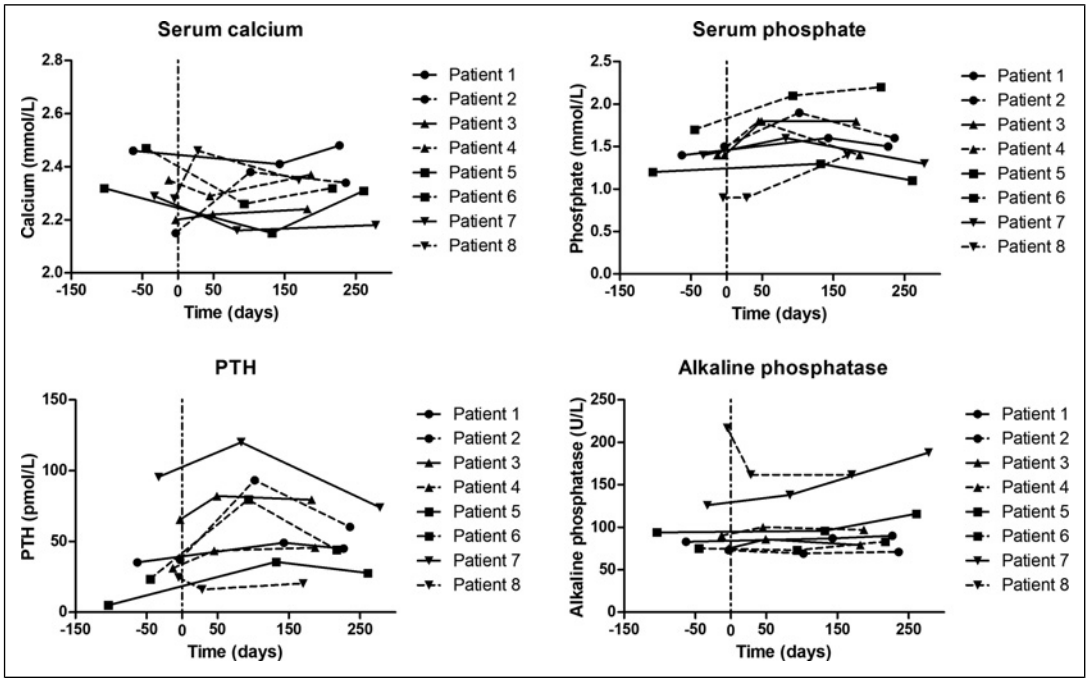

Fig. 1. Change in bone mineral parameters over time for each patient.

Table 2. Bone mineral laboratory parameters over time

	Tbaseline	Tpost	T6months	*p* value
Calcium, mmol/L	2.32±0.11	2.29±0.12	2.32±0.09	0.735
Phosphate, mmol/L	1.36±0.23	1.63±0.38	1.54±0.34	0.024*
PTH, pmol/L	39.63±28.27	64.85±34.46	49.54±20.72	0.008*
Alkaline phosphatase, U/L	104.1±48.8	101.4±32.4	110.7±42.4	0.56

Laboratory values represent means ± standard deviation.

Tbaseline: 3 ± 8 weeks prior to change in PD fluids, Tpost: 6 ± 6 weeks after change in PD fluids, T6months: 24 ± 9 weeks after change in PD fluids. *Significant differences between the three timepoints.

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Table 3. Prescription of phosphate binders

	Tbaseline	Tpost	T6months	*p* value
Calcium-free phosphate binders (tablets)	1.50 [0.00–3.00]	1.50 [0.00–3.00]	1.50 [0.00–3.75]	1.000
Calcium-based phosphate binders (tablets)	1.00 [0.00–2.75]	1.00 [0.00–4.00]	3.50 [2.00–5.50]	0.004[a]
Mean calcium content, mg	151±175	206±238	371±227	0.001
Cinacalcet, %	0	0	37.5	0.050
Vitamin D analogs, %	100	100	100	

[a]Significant differences between Tbaseline and T6months ($Z = -2.23$, $p = 0.026$) and Tpost and T6months ($Z = -2.26$, $p = 0.024$).

subgroup analysis by study design (randomized controlled trial and non-randomized controlled trial). They concluded that calcium levels decreased after lowering the calcium concentration in the PD fluids from 1.75 mmol/L to 1.25 mmol/L. Moreover, iPTH levels were significantly lower with 1.75 mmol/L dialyzate calcium as compared to 1.25 mmol/L. However, none of the studies included in this meta-analysis investigated the role of icodextrin 7.5% on the observed calcium changes. Our hypothesis that the use of icodextrin 7.5% for the once-daily long dwell attenuates changes in calcium and iPTH concentrations have, to the best of our knowledge, never been studied. As compared to the data from the abovementioned meta-analysis [19], we did not observe significant changes in total serum calcium, while the meta-analysis showed otherwise. Regarding iPTH, in our study, a temporal rise in iPTH levels was observed, but this rise was significantly less prominent as compared to some of the previous studies in which no icodextrin 7.5% dwell was prescribed. For example, Sanchez et al. [17] noted a rise in iPTH of 47% (from 226.2 ± 228 to 332 ± 188.7) and Sun et al. [22] noted a rise of 54% (from 124.5 ± 16.7 to 191.9 ± 114.7). In our study, the increase was 25% (from 39.63 ± 28.27 to 49.54 ± 20.72). In our case series, AF levels remained stable, which is in line with a previous study [23].

Phosphate levels increased after intervention, which could not be well explained. Possibly it was normal variation augmented by the small sample size. However, subsequently, we observed an increase in the prescription of calcium-based phosphate binders, while prescription of calcium-free remained stable. It is plausible that the treating physician preferred calcium-containing binders over calcium-free binders due to rising iPTH levels and calcium levels in the low-normal range.

The study is limited by the small sample size, and it is uncontrolled and observational character. No additional laboratory samples were drawn, other than those for routine clinical care. The change in calcium concentration in the PD fluids in this study was driven by the fact that PD fluids with high calcium levels were withdrawn from the market in the Netherlands. The present study suggests that it appears safe to reduce calcium levels, thereby likely avoiding a positive calcium balance with potential harmful effects. It has been shown previously that a rise in PTH can be well managed with calcium-containing phosphate binders or calcimimetics [23]. Although robust data on calcium balance and clinical outcome in PD patients are lacking, conservative use of high calcium-containing PD fluids seems appropriate. In conclusion, the use of icodextrin for the once-daily long dwell appears to have an attenuating effect on bone mineral parameters when calcium content of PD fluid is changed from a high (1.75 mmol/L) to a low (1.25 mmol/L) calcium concentration. Although changes in serum calcium appear negligible, a rise in iPTH should be anticipated. A timely increase in calcium prescription via phosphate binders can help restore calcium balance, preventing

progressive hyperparathyroidism, high bone turnover, and hyperphosphatemia. More studies are needed to address the role of icodextrin in bone mineral parameters in PD patients and its effect on clinical outcomes.

Statement of Ethics

This study protocol was reviewed, and the need for approval was waived by the Scientific Committee of the Northwest Clinics, Alkmaar, The Netherlands. Written informed consent was obtained from the patients for publication of the details of their medical case and any related data from their electronic hospital files.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Lara Verschuur and Anouschka Liefting collected the data. Lara Verschuur was responsible for the data analysis and wrote the draft version of this manuscript. Bastiaan van Dam, Erik Penne, and Fenneke Frerichs contributed to reviewing, editing, and revising of the manuscript. Erik Penne was responsible for the final revisions. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Beladi Mousavi SS, Saghafi H. Renal bone disease among patients with ESRD. Nephrourol Mon. 2013;5(3):849–50.
2 de Oliveira RA, Barreto FC, Mendes M, dos Reis LM, Castro JH, Britto ZML, et al. Peritoneal dialysis per se is a risk factor for sclerostin-associated adynamic bone disease. Kidney Int. 2015;87(5):1039–45.
3 Wang AYM, Woo J, Wang M, Sea MMM, Ip R, Li PKT, et al. Association of inflammation and malnutrition with cardiac valve calcification in continuous ambulatory peritoneal dialysis patients. J Am Soc Nephrol. 2001;12(9):1927–36.
4 Chuang S, Wong H, Vathsala A, Lee E, How PPC. Prevalence of chronic kidney disease-mineral and bone disorder in incident peritoneal dialysis patients and its association with short-term outcomes. Singapore Med J. 2016;57(11):603–9.

5 Noordzij M, Korevaar JC, Bos WJ, Boeschoten EW, Dekker FW, Bossuyt PM, et al. Mineral metabolism and cardiovascular morbidity and mortality risk: peritoneal dialysis patients compared with haemodialysis patients. Nephrol Dial Transpl. 2006;21(9):2513–20.
6 Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, et al. Predictors and consequences of altered mineral metabolism: the dialysis outcomes and practice patterns study. Kidney Int. 2005;67(3):1179–87.
7 Fouque D, Roth H, Pelletier S, London GM, Hannedouche T, Jean G, et al. Control of mineral metabolism and bone disease in haemodialysis patients: which optimal targets? Nephrol Dial Transpl. 2013;28(2):360–7.
8 Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, et al. Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding. Am J Kidney Dis. 2014;63(6):979–87.
9 Lacson E, Wang W, Hakim RM, Teng M, Lazarus JM. Associates of mortality and hospitalization in hemodialysis: potentially actionable laboratory variables and vascular access. Am J Kidney Dis. 2009;53(1):79–90.
10 Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. Nephrol Dial Transplant. 2011;26(6):1948–55.
11 Markaki A, Kyriazis J, Stylianou K, Fragkiadakis GA, Perakis K, Margioris AN, et al. The role of serum magnesium and calcium on the association between adiponectin levels and all-cause mortality in end-stage renal disease patients. PLoS One. 2012;7(12):e52350.
12 Fein PA, Asadi S, Singh P, Hartman W, Stuto S, Chattopadhyay J, et al. Relationship between alkaline phosphatase and all-cause mortality in peritoneal dialysis patients. Adv Perit Dial. 2013;29:61–3.
13 Coen G, Pierantozzi A, Spizzichino D, Sardella D, Mantella D, Manni M, et al. Risk factors of 1 year increment of coronary calcifications and survival in hemodialysis patients. BMC Nephrol. 2010;11:10.
14 Spasovski G, Gelev S, Masin-Spasovska J, Selim G, Sikole A, Vanholder R. Improvement of bone and mineral parameters related to adynamic bone disease by diminishing dialysate calcium. Bone. 2007;41(4):698–703.
15 Ok E, Asci G, Bayraktaroglu S, Toz H, Ozkahya M, Yilmaz M, et al. Reduction of dialysate calcium level reduces progression of coronary artery calcification and improves low bone turnover in patients on hemodialysis. J Am Soc Nephrol. 2016;27(8):2475–86.
16 Slatopolsky E, Weerts C, Norwood K, Giles K, Fryer P, Finch J, et al. Long-term effects of calcium carbonate and 2.5 mEq/liter calcium dialysate on mineral metabolism. Kidney Int. 1989;36(5):897–903.
17 Sanchez C, Lopez-Barea F, Sanchez-Cabezudo J, Bajo A, Mate A, Martínez E, et al. Low vs standard calcium dialysate in peritoneal dialysis: differences in treatment, biochemistry and bone histomorphometry. A randomized multicentre study. Nephrol Dial Transpl. 2004;19(6):1587–93.
18 (KDIGO) CKDMBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;113:S1–130.
19 Jin L, Zhou J, Shao F, Yang F. Long-term effects on PTH and mineral metabolism of 1.25 versus 1.75 mmol/L dialysate calcium in peritoneal dialysis patients: a meta-analysis. BMC Nephrol. 2019;20(1):213.
20 Weinreich T, Ritz E, Passlick-Deetjen J, Colombi A, Echterhoff H, Geberth S, et al. Long term dialysis with low-calcium solution (1.0 Mmol/L) in capd: effects on bone mineral metabolism. Perit Dial Int. 1996;16(3):260–8.
21 Moraes TP, Bucharles SGE, Ribeiro SC, Frumento R, Riella MC, Pecoits-Filho R. Alteração do teor de cálcio no banho de DP para 2.5 mEq/L é eficaz no reestabelecimento dos valores preconizados por diretrizes atuais em pacientes com PTH <150 pg/dL. J Bras Nefrol. 2010;32(3):275–80.
22 Sun J, Wang R, Yu K, Wang Q, Wang X. The effect of low calcium dialysate on calcium-phosphate metabolism and its correlation with other coefficient factors in CAPD. Dial Transplant. 2009;38(8):320–3.
23 Piraciaba MCT, Cordeiro L, Guimarães EA, Abensur H, Pereira BJ, Jorgetti V, et al. A feasibility study of avoiding positive calcium balance and parathyroid hormone increase in patients on peritoneal dialysis. Bone Rep. 2022;17(17):101625.