Effects of Lowering Dialysate Calcium Concentration on Mineral Metabolism and Hemodynamic Parameters in Hemodialysis Patients

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Original Paper

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Introduction. It has been suggested that a dialysate calcium concentration of 1.5 mmol/L is a compromise between bone protection and cardiovascular risk. This study aimed to investigate the effect of reducing dialysate calcium concentration to 1.5 mmol/L on mineral metabolism and hemodynamic parameters.
Materials and Methods. Dialysate calcium concentration was changed from 1.75 mmol/L to 1.5 mmol/L for 9 months and observed the effects on mineral metabolism and dialysis outcome parameters in 52 hemodialysis patients.
Results. The results at 9 months demonstrated that postdialytic serum calcium level decreased significantly from 109 ± 7 mg/L to 102 ± 6 mg/L, intact parathyroid hormone (PTH) increased from 372 ± 52 pg/mL to 606 ± 80 pg/mL, and the oral alfacalcidol increased from 1.4 ± 0.3 µg/w to 3.3 ± 0.4 µg/w. In patients with low PTH levels, continuous increase of PTH was observed. There were no significant variation in the oral calcium carbonate dose and serum levels of alkaline phosphatase, predialytic calcium, and pre- and postdialytic phosphorus. The ultrafiltration rate and postdialysis systolic blood pressure were significantly lower after reducing the dialysate calcium concentration to 1.5 mmol/L. Intradialytic hypotension and cramps were more frequent with this dialysate calcium concentration.
Conclusions. These findings demonstrated that a decrease in dialysate calcium concentration from 1.75 mmol/L to 1.5 mmol/L improved mineral metabolism by prevention of postdialytic hypercalcemia and releasing oversuppression of PTH, but it was associated with more use of oral alfacalcidol and more hemodynamic impairment.

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INTRODUCTION

The dialysate calcium concentration for hemodialysis patients can be adjusted to manage more optimally the body's calcium and phosphate balance, and thus improve bone metabolism as well as reduce accelerated arteriosclerosis and cardiovascular mortality. The appropriate dialysate calcium concentration allowing this balance should be prescribed to each individual patient depending on a multitude of variable factors relating to calcium load.

A lower dialysate calcium concentration of 1.25 mmol/L to 1.3 mmol/L will permit the use of vitamin D supplements and calcium-based phosphate binders in clinical practice, with

much less risk of calcium loading and resultant hypercalcemia and calcification. Low dialysate calcium concentrations are useful in the setting of adynamic bone disease where an increase in bone turnover is required. However, low calcium levels in the dialysate may also predispose to cardiac arrhythmias and hemodynamically unstable dialysis sessions with intradialytic hypotension.[1,2] Higher dialysate calcium concentrations are useful to sustain normal serum calcium levels where patients are not taking calcium-based binders or if calcium supplements are not able to normalize serum levels.

Suppression of hyperparathyroidism is also effective with a dialysate calcium level of 1.75 mmol/L, but hypercalcemia, metastatic calcification, and oversuppression of parathyroid hormone are the risks.[1-3] Dialysate calcium concentration of 1.5 mmol/L may be a compromise between bone protection and reduction in cardiovascular risk for conventional hemodialysis and is a common concentration used throughout the world.[1,2] In this study, we examined the effect of lowering calcium concentration of dialysate from 1.75 mmol/L to 1.5 mmol/L on bone metabolism and cardiovascular stability during hemodialysis sessions.

MATERIALS AND METHODS

Patients Parameters

In this prospective study, 52 hemodialysis patients were treated by lowering dialysate calcium from 1.75 mmol/L to 1.5 mmol/L. The total observation period after changing dialysate concentration was 9 months (from October 2009 to Jul 2010). Adynamic bone disease was assessed according to the definition of a normal serum alkaline phosphatase level and a serum intact parathyroid hormone (PTH) less than 150 pg/mL.

Study Design

During the study, there was no change in dialysis therapy except that dialysate calcium concentration was lowered from 1.75 mmol/L to 1.5 mmol/L. Calcium carbonate or sevelamer were given as phosphate binders. Alphacalcidiol was applied to stabilize serum concentration of calcium, and intact PTH. Ergocalciferol was used to correct the level of 25-hydroxyvitamin D. The last laboratory measurements of the study period with 1.75 meq/L of dialysate calcium served as baseline data. Laboratory measurements were repeated every 3 months, up to 9 months, after switching dialysate calcium concentration. Routine laboratory parameters were measured by standard biochemical methods. Intact PTH was measured with chimiluminescence. Dialytic parameters including blood pressure, heart rate, ultrafiltration rate, interdialytic weight gain, and intradialytic complications were also recorded in the same group of patients with dialysate calcium concentration at 1.75 mmol/L (2400 hemodialysis sessions) and at 1.50 mmol/L (2000 hemodialysis sessions) during the two intervals of 4 months.

Statistical Analyses

Statistical analyses were done using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA). All descriptive data were expressed as mean ± standard error of mean or percentage. The Student *t* test and the 1-way analysis of variance with repeated measures were used for comparison of quantitative parameters and the chi-square test for qualitative parameters. A value of *P* less than .05 was considered significant.

RESULTS

Fifty-two hemodialysis patients (mean age, 56 ± 13 years; 19 women and 33 men) were included in the study. End-stage renal failure was due to vascular nephropathy (11.0%), interstitial nephropathy (4.2%), chronic glomerulonephritis (3.8%), diabetic nephropathy (32.0%), and unknown origin (49.0%). The patients had been on hemodialysis for 71 ± 60 months for 4 hour, 3 times weekly. Before switching the dialysate calcium concentration, 14% of the patients had adynamic bone disease. The demographic data, primary diseases, and biological and clinical parameters of the enrolled patients are described in Table 1.

Two patients were excluded from the study; 1 patient was transferred to another center and another received a parathyroidectomy. Therefore, 50 patients completed the study. After reducing dialysate calcium concentration from 1.75 mmol/L to 1.5 mmol/L, postdialytic serum calcium level decreased significantly ($P < .001$) from 109 ± 7 at baseline to 102 ± 2 mg/L after 9 months (Table 2). But predialytic calcium level remained stable and was still not significantly different compared with

Table 1. Baseline Data of the Enrolled Hemodialysis Patients

Parameter	Value
Sex, n	
Female	19
Male	33
Age, y	56 ± 13 (33 to 81)
Dialysis duration, mo	71 ± 60 (8 to 301)
Cause of kidney failure, %	
Vascular nephropathy	11.0
Interstitial nephropathy	4.2
Chronic glomerulonephritis	3.8
Diabetic nephropathy	32.0
Unknown origin	49.0
Albumin, g/dL	42.8 ± 3.0
β2-microglobulin, mg/mL	36 ± 11
Aluminemia, µmol/L	0.98 ± 0.37
25-hydroxyvitamin D3, nmol/L	22 ± 10

the initial level after the intervention.

As shown in the Figure 1, reducing dialysate calcium concentration increased the intact PTH levels significantly (P = .01) from baseline 372 ± 52 pg/mL to a maximum of 606 ± 80 pg/mL at 9 months. In patients with adynamic bone disease before the intervention, continuous increase of intact PTH level was observed (from 93 ± 9 pg/mL to 284 ± 52 pg/mL; P = .002; Figure 2). Despite increasing doses of oral alfacalcidol (from 1.4 ± 0.3 µg/w to 3.3 ± 0.4 µg/w, P = .005), the doses of calcium carbonate did not change. As determined by the univariate regression analysis, PTH showed a significant positive correlation with oral alfacalcidiol (R^2 = 0.53, P < .001).

The number of patients with calcimimetic drugs increased from 3 to 5 at the end of the study. After 9 months, serum levels of phosphate,

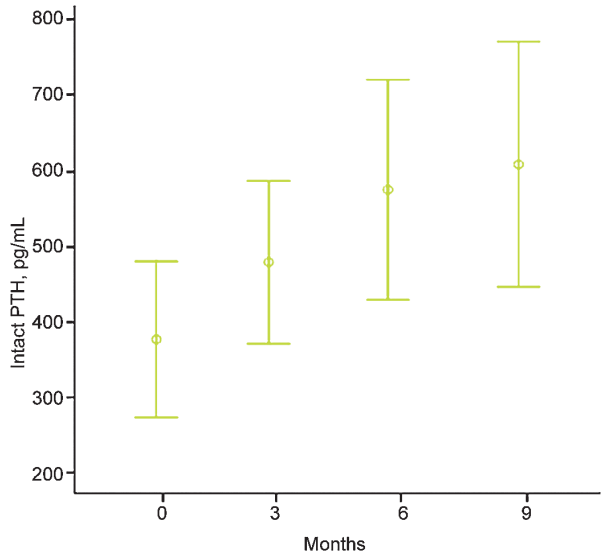

Figure 1. Impact of lowering dialysate calcium concentration parathyroid hormone (PTH) in 9 months.

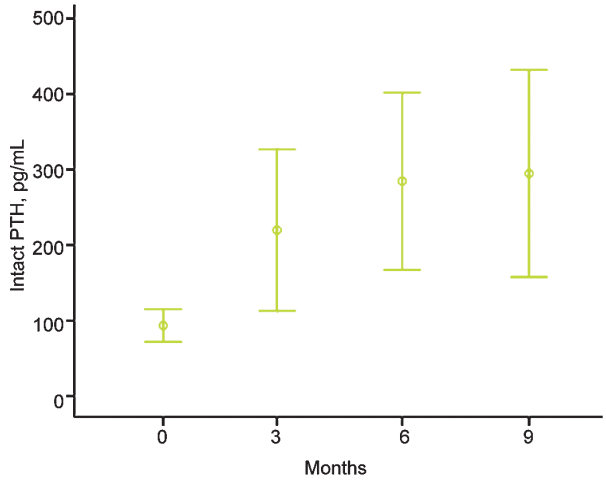

Figure 2. Impact of lowering dialysate calcium concentration on parathyroid hormone (PTH) in patients with low intact PTH level at baseline.

Table 2. Studied Parameters at Baseline and After Lowering Dialysate Calcium Concentration

Parameter	Baseline	3 Months	6 Months	9 Months
Predialytic calcium, mg/L	89 ± 8	90 ± 7	88 ± 8	89 ± 12
Postdialytic calcium, mg/L	109 ± 7	99 ± 7*	100 ± 6*	102 ± 6*
iPTH, pg/mL	372 ± 52	383 ± 54	507 ± 7 3†	606 ± 80‡
Predialytic phosphorus, mg/L	43 ± 13	45 ± 12	46 ± 15	47 ± 15
Postdialytic phsoph, mg/L	23 ± 7	21 ± 5	21 ± 6	21 ± 9
Alkaline phosphatase, UI/mL	170 ± 19	169 ± 18	199 ± 27	169 ± 21
Albumin, g/L	42.8 ± 3	42,7 ± 4	42.7 ± 4	43 ± 7
Bicarbonate, mEq/L	21 ± 2	24 ± 3	24.6 ± 3	22 ± 2
25-hydroxyvitamin D, nmol/L	22 ± 10		36 ± 13†	
Oral alfacalcidol dose, µg/w	1.4 ± 0.3	2,1 ± 0,3	2.75 ± 0.4*	3.3 ± 0.4*
Calcium carbonate dose, g/d	0.73 ± 0.4	0,75 ± 0,4	0.74 ± 0.4	0.75 ± 0.4
Sevelamer adminnistration, %	6	14	20†	20†

*P < .005 as compared with baseline
†P < .05 as compared with baseline
‡P < .01 as compared with baseline

Table 3. Hemodynamic Parameters Before and 9 Months After Lowering Dialysate Calcium Concentration

	Dialysate Calcium Concentration		
Parameter	**1.75 mmol/L**	**1.5 mmol/L**	***P***
Predialytic systolic blood pressure, mm Hg	133 ± 24	136 ± 24	.73
Predialytic mean blood pressure, mm Hg	71 ± 16	72 ± 18	.30
Predialytic diastolic blood pressure, mm Hg	93 ± 18	95 ± 18	.30
Interdialytic weight gain, kg	2.8 ± 0.2	3.1 ± 0.3	.40
Ultrafiltration rate, mL/h	579 ± 242	521 ± 238	< .001
Sessions with symptomatic hypotension, %	10	13	.04
Sessions with cramps, %	2.7	4.0	.01
Postdialytic systolic blood pressure, mm Hg	132 ± 24	128 ± 22	.002
Postdialytic mean blood pressure, mm Hg	93 ± 18	89 ± 17	.07
Postdialytic diastolic blood pressure, mm Hg	70 ± 15	68 ± 16	.15
Heart rate before dialysis, bpm	76 ± 16	76 ± 15	.90
Heart rate after dialysis, bpm	79 ± 17	80 ± 17	.64

predialytic calcium, alkaline phosphatase, albumin and bicarbonate were not changed. Changes in the systolic, mean, and diastolic blood pressure measures, heart rate, ultrafiltration rate, interdialytic weight gain, and frequency of symptomatic hypotension and cramps during dialysis are shown in Table 3. After switching dialysate calcium concentration, postdialysis systolic blood pressure was significantly lower (132 ± 24 mm Hg at baseline versus 128 ± 22 mm Hg after the intervention, $P = .002$). Ultrafiltration rate decreased significantly after reducing dialysate calcium concentration (from 579 ± 242 mL/h to 521 ± 238 mL/h; $P < .001$). Symptomatic hypotension and cramps were more frequent with lower calcium concentration (13% versus 10%, $P = .04$ and 4% versus 2.7%, $P = .01$, respectively). In contrast, there were no significant differences in the predialysis blood pressures, interdialytic weight gain, and heart rates before and after the intervention.

DISCUSSION

Recent changes in the management of mineral metabolism in hemodialysis patients have placed more emphasis on the concentration of calcium in dialysate which is the main variable affecting dialysis calcium balance.[4] Worldwide use of dialysate calcium varies throughout different countries, and there is still much debate on what the ideal dialysate calcium concentration should be (null, positive, or negative calcium balance). The Kidney Disease: Improvement of Global Outcomes guideline for dialysate calcium suggests a narrow range of dialysate inlet calcium concentrations of 1.25 mEq/L to 1,50 mEq/L.[5] Whereas in Japan and Australia, a dialysate of 1.5 mmol/L is common.[1]

In chronic dialysis patients, the calcium balance is the result of net calcium absorption from the intestine, calcium excretion via residual urinary output, calcium loss through the skin in case of transpiration, and net calcium transfer during each dialysis session. The net calcium balance during a dialysis session depends on the diffusion gradient between the ultrafilterable calcium concentration in the blood and that of the dialysis fluid, the dialysance of calcium, the ultrafiltration rate, and the duration of the session.[6] A gain of calcium is generally expected when the dialysate calcium is greater than 1.5 mmol/L.[7]

Several studies have shown that the use of total dialysate calcium of 1.5 mmol/L may be beneficial because balance values of total dialysate calcium are slightly positive, but serum concentration of ionized calcium stays in the normal range.[8,9] Interestingly, reports from the Dialysis Outcomes And Practice Patterns Study data showed there was a significantly increased all-cause mortality risk associated with a higher calcium dialysate.[10,11]

In our study differences in serum markers of mineral metabolism between 1.5 mmol/L and 1.75 mmol/L were observed. Postdialysis calcium levels were significantly higher with 1.75-mmol/L dialysate calcium. This has been demonstrated by others.[7,12,13] Low calcium dialysate was shown to induce a clinically significant increase in PTH level.[14,15] As seen in others studies, this may be beneficial in patients with adynamic bone disease and low serum PTH levels.[16,17] However, this may exacerbate the hyperparathyroidism in hemodialysis patient.[18] In contrast, no change was observed in

the alkaline phosphatase level and in the dose of calcium carbonate. This may be explained by 2 confounding factors: the increasing of the doses of oral alfacalcidiol and the use of phosphate binders. This was required to maintain the serum phosphate level and predialytic calcium.

It has long been known that higher dialysate calcium, compared with a low, dialysate calcium concentration is associated with better hemodynamic stability during the hemodialysis session.[19,20] Also, the increase of intracellular calcium is one of probable factors for hypertension in hemodialysis patients.[3] We confirmed in our study that the concentration of calcium in the dialysis fluid have significant repercussions during hemodialysis. Whereas the European Best Practice Guidelines suggest the use of a dialysate calcium concentration of 1.50 mmol/L in patients with frequent episodes of intadialytic hypotension.[21] As expected, a decrease in blood pressure and more frequent intradialytic hypotension episodes were observed using dialysate calcium concentration of 1.5 mmol/L versus 1.75 mmol/L.[22]

Blood pressure may be altered by changes in calcium either through alterations in systemic vascular resistance or changes in cardiac output, or both.[1] During dialysis, serum ionized calcium level, which is a determinant of vasoconstriction and cardiac output, changes directly with the dialysate calcium concentration and may impact hemodynamic stability on dialysis.[23-25] One study looking at the effect of treatment with lower dialysate calcium revealed favorable changes in blood pressure and arterial compliance as well as a reduction in serum aldosterone levels (a marker of vasoactivity).[26] A study of 8 hemodialysis patients with variable dialysate calcium level from 0.5 mmol/L to 2.5 mmol/L concluded that the effect of serum calcium on blood pressure was through left ventricular stroke volume and output.[27]

The limitations of our study were the small number of the study population and the heterogeneity of the causes of end-stage renal disease. Also, we did not study the vascular calcifications and other bone turnover markers.

CONCLUSIONS

The optimal calcium concentration of the dialysis fluid must be a compromise between the need to guarantee cardiovascular stability during the hemodialysis sessions and the goal to maintain normal bone turnover and mineralization in order to avoid bone pain and fractures.

CONFLICT OF INTEREST

None declared.

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