Effect of Low Dialysate Calcium on Clinical Outcomes in Hemodialysis Patients in the United States

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Introduction

- The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that dialysate calcium concentrations be 1.25 mmol/L for most patients undergoing hemodialysis for the treatment of ESRD.[1,2]
- Some dialysis clinics in the United States have reduced dialysate calcium concentration from 1.25 mmol/L to 1.125 or 1.000 mmol/L, presumably to avoid calcium overload.
- To date, there has been no rigorous systematic examination of the effects of low dialysate calcium on clinical outcomes.

Objective

The following study examined the association between conversion from predominant use (>75% patients) of 1.25 mmol/L dialysate calcium bath to predominant use of 1.125 or 1.000 mmol/L (converter clinics) versus those that maintained predominant use of 1.25 mmol/L dialysate calcium (control clinics) and relevant clinical outcomes, laboratory markers of metabolic bone disease, and related drug utilization at the facility level.

Methods

Source Data

- We conducted a retrospective study of in-center hemodialysis clinics at a large dialysis organization (LDO) from 01 January 2008 through 31 December 2010.
- Patient characteristics were abstracted from the LDO's electronic health record.
- Data on clinical events were abstracted by linkage to Medicare Part A claims data from the United States Renal Data System (USRDS) data. Because oral medication utilization data are only available for Medicare Part D beneficiaries, secondary analyses of laboratory outcomes and injected medication utilization were conducted among the subgroup of patients with Part D benefits. Cause-specific hospitalization events were ascribed based on the Primary International Classification of Diseases, ninth revision diagnosis on the respective claims.
- Hypocalcemia was defined using 3 increasingly restrictive definitions: serum calcium < 2.100 mmol/L, < 2.000 mmol/L, and < 1.875 mmol/L, whereas hypercalcemia was defined as serum calcium > 2.55 mmol/L.
- Intradialytic hypotension was defined as a fall in systolic blood pressure of at least 20 mm Hg accompanied by at least 2 responsive measures (premature cessation of dialysis, saline administration, reduction in blood flow rate, and reduction in ultrafiltration rate).

Converter and Control Facilities

- Converter and control clinics were matched (1:many, with replacement) on the basis of mean age, percent incident patients, geography, and clinic length of ownership.
- Data were considered in 2 periods: preconversion and postconversion (Figure 1).
  - For converter facilities the preconversion period was the most antecedent window (of at least 3 and up to 6 months) during which there was predominant use of 1.25 mmol/L dialysate calcium.
  - The postconversion period was the contiguous window (of at least 3 and up to 12 months) beginning on the first date of the first month (ie, month 0) in which there was predominant use of < 1.25 mmol/L dialysate calcium (index date) and continuing until end of study or until the facility no longer used < 1.25 mmol/L calcium dialysate predominantly; periods need not have been consecutive.
  - For control facilities the index month was randomly assigned based on a distribution that mirrored that of index months among converter facilities.

Analysis

- Mixed linear models were fit to assess change in event rates pre- to postconversion among converter clinics versus contemporaneous change in control clinics. Results were expressed as relative rate ratios (RRRs) (values > 1 indicate greater rate among converters) or as delta-delta (values > 0 indicate higher values among converters).
- Responses were estimated separately for postconversion months 0-2 and 3+ to allow for possible latent effects.

Figure 1. Pre- and Postconversion Schematic for Converter vs Control Facilities

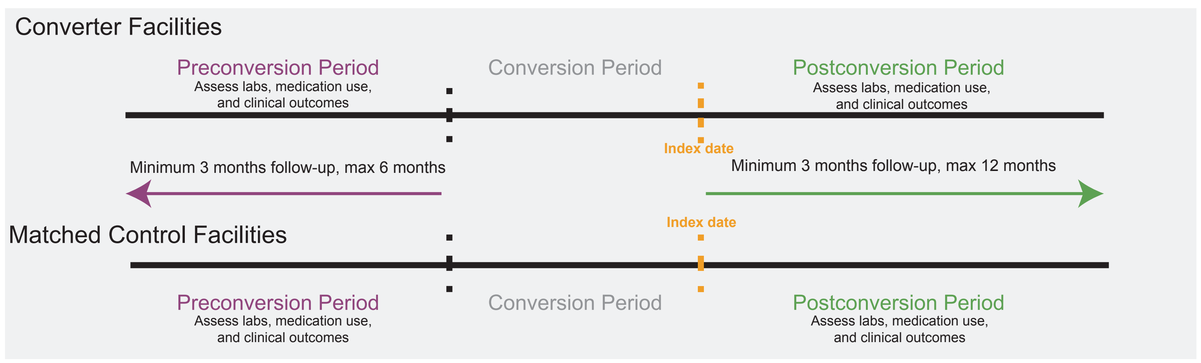


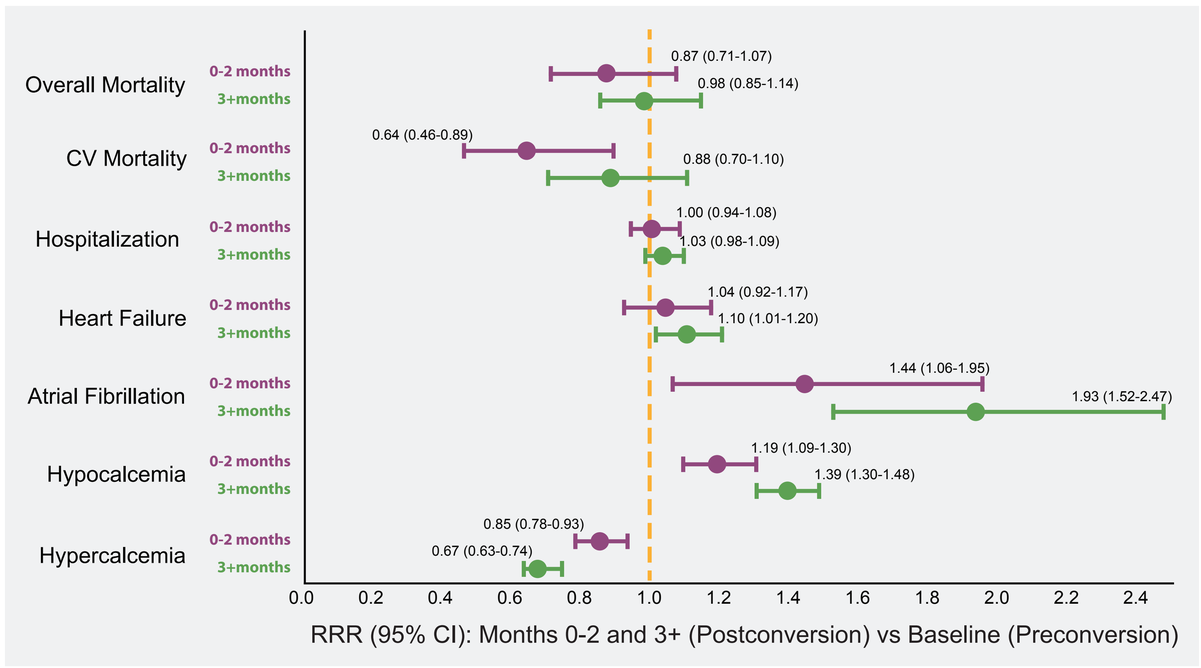
Table 1. Comparison of Converter and Control Facilities at Index Time[a]

Facility	Matched Control Facilities (N=274)	Matched Converter Facilities (N=79)	P[b]
Age, years*			0.47
Mean ± SD	62.22 ± 3.55	62.551 ± 4.14	
Median [p25, p75]	62.02 [59.32, 64.46]	61.71 [59.61, 65.34]	
Incident patients*			0.42
Mean ± SD	10% ± 5%	9% ± 5%	
Median [p25, p75]`	10% [7%, 12%]	9% [6%, 12%]	
Race/Ethnicity			0.40
Black			0.40
Mean ± SD	30% ± 29%	26% ± 27%	
Median [p25, p75]	20% [5%, 52%]	16% [5%, 41%]	
Hispanic			0.63
Mean ± SD	15% ± 21%	14% ± 22%	
Median [p25, p75]	5% [1.0%, 20%]	5% [0%, 18%]	
White			0.63
Mean ± SD	49% ± 30%	51% ± 32%	
Median [p25, p75]	43% [24%, 73%]	52% [23%, 80%]	
Other			0.32
Mean ± SD	6% ± 8%	9% ± 16%	
Median [p25, p75]	3% [0%, 8%]	4% [1%, 11%]	
Female			0.63
Mean ± SD	44% ± 8%	45% ± 8%	
Median [p25, p75]	44% [40%, 49%]	46% [39%, 49%]	
Sp-Kt/V			
Mean ± SD	1.67 ± 0.09	1.70 ± 0.11	0.11
Median [p25, p75]	1.66 [1.61, 1.72]	1.68 [1.61, 1.75]	
Vintage, months			0.08
Mean ± SD	42.35 ± 8.88	40.24 ± 9.39	
Median [p25, p75]	42.15 [36.22, 48.08]	39.80 [32.90, 46.10]	
Serum calcium, mmol/L			0.10
Mean ± SD	2.27 ± 0.05	2.28 ± 0.06	
Median [p25, p75]	2.27 [2.24, 2.29]	2.27 [2.25, 2.32]	
Serum phosphorus, mmol/L			< 0.001
Mean ± SD	1.64 ± 0.10	1.69 ± 0.10	
Median [p25, p75]	1.64 [1.58, 1.70]	1.70 [1.61, 1.77]	
Parathyroid hormone, ng/L			
Mean ± SD	338.97 ± 82.86	358.02 ± 87.39	0.09
Median [p25, p75]	329.88 [273.30, 395.37]	352.02 [289.73, 400.50]	
AVDA use			0.95
Mean ± SD	77% ± 11%	78% ± 10%	
Median [p25, p75]	79% [71%, 85%]	79% [74%, 85%]	
Cardiac arrest			0.57
Mean ± SD	0.15% ± 0.01%	0.11% ± 0.01%	
Median [p25, p75]	0.00% [0.00%, 0.00%]	0.00% [0.00%, 0.00%]	
Cerebrovascular diagnosis			0.49
Mean ± SD	2% ± 3%	2% ± 3%	
Median [p25, p75]	1% [0%, 3%]	0% [0%, 0%]	
Congestive heart failure			0.54
Mean ± SD	11% ± 12%	11% ± 11%	
Median [p25, p75]	7% [4%, 14%]	8% [3%, 14%]	
Coronary heart disease			0.18
Mean ± SD	10% ± 13%	8% ± 11%	
Median [p25, p75]	5% [2%, 14%]	4% [2%, 12%]	
Myocardial infarction			0.77
Mean ± SD	0.17% ± 0.01%	0.17% ± 0.01%	
Median [p25, p75]	0.00% [0.00%, 0.00%]	0.00% [0.00%, 0.00%]	
Peripheral vascular disease			0.65
Mean ± SD	3% ± 5%	2% ± 4%	
Median [p25, p75]	1% [0%, 3%]	1% [0%, 3%]	
Charlson Comorbidity Index Score			0.66
Mean ± SD	5.71 ± 0.55	5.65 ± 0.55	
Median [p25, p75]	5.57 [5.30, 6.04]	5.54 [5.33, 5.96]	

[a] Index time defined as first full month following conversion for converter facilities; randomly assigned to control facilities in the matching process.
[b] Comparisons made by 2-tailed Wilcoxon rank sum test.
* Variables used in the matching algorithm. Facilities were also matched on geographic region and facility length of ownership (both perfectly balanced in matched population; not shown).
Abbreviations: AVDA, activated vitamin D analog; ESRD, end-stage renal disease; SD, standard deviation; sp-Kt/V, single pool dialysis adequacy

Results

Figure 2. Comparison of Clinical Outcomes Among Converter vs Control Facilities



Abbreviations: CI, confidence interval; CV, cardiovascular; RRR, relative risk ratio

- Converter and control clinics were well balanced for case mix (Table 1).
- Figure 2 shows the clinical outcomes among converter facilities versus control facilities.
  - No differences were observed in rates of all-cause mortality or hospitalization.
  - Patients in converter clinics experienced greater risk of heart failure exacerbation, atrial fibrillation, and hypocalcemia (serum calcium < 2.000 mmol/L) (Figure 2). Similar findings were seen when other definitions of hypocalcemia were considered (not shown).
  - Risk of intradialytic hypotension was also greater among patients in converter versus control clinics: RRR (95% CI) 1.05 (1.03-1.07). Intradialytic hypotension was fit with only a pre/postconversion specification (2 time periods, not 3 time periods) due to the frequency of the outcome and nonconvergence in the 3-period model.
- Table 2 shows laboratory and medication utilization data. Compared to control clinics, converter clinics experienced:
  - Decreased serum calcium
  - Increased serum phosphate and parathyroid hormone
  - Increased utilization of phosphate binders, activated vitamin D, and calcimimetics

Table 2. Biochemical Changes and Medication Utilization Across Dialysate Calcium Conversion Time Periods

		Preconversion Months -3 to -1		Postconversion Months 0 to 2		Postconversion Months 3+	
		Control	Converter	Control	Converter	Control	Converter
Biochemical Changes							
Calcium	Mean (mmol/L)	2.28	2.30	2.27	2.27	2.26	2.25
	Difference	0 (ref)	0.02 ± 0.02 p < 0.001	0 (ref)	0.00 ± 0.02 p = 0.10	0 (ref)	-0.01 ± 0.02 p = 0.02
	ΔΔ	REF		-0.02 ± 0.01 p < 0.001		-0.03 ± 0.01 p < 0.001	
Phos	Mean (mmol/L)	1.66	1.69	1.63	1.70	1.61	1.65
	Difference	0 (ref)	0.03 ± 0.03 p = 0.004	0 (ref)	0.07 ± 0.03 p < 0.001	0 (ref)	0.04 ± 0.03 p < 0.001
	ΔΔ	REF		0.04 ± 0.02 p < 0.001		0.01 ± 0.02 p = 0.002	
PTH	Mean (ng/L)	351	359	344	376	346	366
	Difference	0 (ref)	7.54 ± 7.59 p = 0.32	0 (ref)	32.04 ± 8.08 p < 0.001	0 (ref)	20.34 ± 7.06 p = 0.004
	ΔΔ	REF		24.50 ± 5.74 p < 0.001		12.80 ± 4.19 p = 0.002	
Alk Phos	Mean (U/L)	108	113	105	111	101	106
	Difference	0 (ref)	4.84 ± 1.25 p < 0.001	0 (ref)	5.46 ± 1.31 p < 0.001	0 (ref)	5.54 ± 1.19 p < 0.001
	ΔΔ	REF		0.62 ± 0.80 p = 0.44		0.70 ± 0.59 p = 0.23	
Medication Use							
Non-Ca Binder	Mean (mg/day)	1705	1502	1766	1543	1632	1709
	Difference	0 (ref)	-203 ± 75 p = 0.007	0 (ref)	-224 ± 79 p = 0.005	0 (ref)	77 ± 71 p = 0.28
	ΔΔ	REF		-21 ± 52 p = 0.70		280 ± 38 p < 0.001	
sqrt Ca Binder[a]	Mean (mg/day)	659	561	668	595	599	632
	Difference	0 (ref)	-2.0 ± 0.9 p = 0.02	0 (ref)	-1.4 ± 0.9 p = 0.11	0 (ref)	1.1 ± 0.8 p = 0.20
	ΔΔ	REF		0.5 ± 0.5 p = 0.32		3.1 ± 0.4 p < 0.001	
IV AVDA	Mean (µg/tx)	1.29	1.31	1.31	1.38	1.41	1.63
	Difference	0 (ref)	0.02 ± 0.05 p = 0.62	0 (ref)	0.07 ± 0.05 p = 0.17	0 (ref)	0.22 ± 0.05 p < 0.001
	ΔΔ	REF		0.05 ± 0.02 p = 0.06		0.20 ± 0.02 p < 0.001	
Cinacalcet[b]	Mean (mg/day)	6.60	6.02	6.57	6.36	6.05	6.52
	Difference	0 (ref)	-0.09 ± 0.07 p = 0.20	0 (ref)	-0.03 ± 0.08 p = 0.67	0 (ref)	0.07 ± 0.07 p = 0.29
	ΔΔ	REF		0.06 ± 0.04 p = 0.14		0.17 ± 0.03 p < 0.001	

[a] Analyzed on square root scale; differences and B-interaction on square root scale; means are back-transformed to native scale.
[b] Analyzed on log scale; by definition this only includes facilities with at least some cinacalcet use; differences and B-interaction on log scale; means are back-transformed to native scale.
For Vitamin D, Hectorol = Zemplar dose/2.5 = Calcitriol dose/0.75
Dose is calculated among users.
Abbreviations: Alk Phos, alkaline phosphatase; AVDA, activated vitamin D; Ca, calcium; IV, intravenous; PTH, parathyroid hormone; Phos, phosphorus; REF, reference; sqrt, square root; tx, treatment

Study Limitations

- Selection bias could be present if the choice of dialysate calcium is a function of the prognosis of patients within a particular facility. However, systematic differences between converter and control facilities were not observed.
- Short-term follow-up may limit ability to see full mortality implications of any kind but for cardiovascular disease in particular.
- This was an observational study, thus residual confounding may be present by unmeasured variables.

Conclusions

These findings indicate potential safety concerns with the use of dialysate calcium concentrations < 1.25 mmol/L, and this is in addition to less biochemical control and greater medication utilization that may be required with the use of lower baths. Further study is required to inform the benefits and risks related to the use of low calcium dialysate.

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