Low versus high dialysate calcium concentration in alternate night nocturnal hemodialysis: a randomized controlled trial

Rosemary MASTERSON[1,2], Susan BLAIR[3], Kevan R POLKINGHORNE[3,4], Kenneth K LAU[5], Michael LIAN[1], Boyd J STRAUSS[5], John G MORGAN[6], Peter KERR[3,4], Nigel D TOUSSAINT[1,2]

[1]Department of Nephrology, The Royal Melbourne Hospital, Parkville, Victoria, Australia; [2]Department of Medicine (RMH), The University of Melbourne, Melbourne, Australia; [3]Department of Nephrology, Monash Medical Centre, Clayton, Victoria, Australia; [4]Monash University, Clayton, Victoria, Australia.

1. Department of Nephrology, The Royal Melbourne Hospital, Parkville, Victoria, Australia
2. Department of Medicine, University of Melbourne, Parkville, Victoria, Australia
3. Department of Nephrology, Monash Medical Centre, Clayton, Victoria, Australia
4. Department of Medicine, Monash University, Clayton, Victoria
5. Department of Radiology, Monash Medical Centre, Clayton, Victoria, Australia
6. Department of Cardiology, The Royal Melbourne Hospital, Parkville, Victoria, Australia

Running head: Dialysate calcium in nocturnal hemodialysis

Word Count: *Abstract:* 249 *Main text:* 3559

Corresponding author: Associate Professor Rosemary Masterson

Department of Nephrology, Royal Melbourne Hospital,

Grattan Street, Parkville, Victoria 3050, Australia.

E-mail: Rosemary.Masterson@mh.org.au

The authors of this paper declare no conflicts of interest and declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

Abstract

Introduction: Higher calcium dialysate is recommended for quotidian nocturnal hemodialysis (NHD) (≥6 nights/week) to maintain bone health. It is unclear what the optimal calcium dialysate concentration should be for alternate night NHD. We aimed to determine the effect of low calcium (LC) versus high calcium (HC) dialysate on cardiovascular and bone parameters in this population.

Methods: A randomized controlled trial where participants were randomized to LC (1.3mmol/L, n=24) or HC dialysate (1.6 or 1.75mmol/L, n=26). Primary outcome was change in mineral metabolism markers. Secondary outcomes included change in vascular calcification (VC) scores (CT abdominal aorta (AA) and superficial femoral arteries (SFA)), pulse wave velocity (PWV), bone mineral density (BMD) and left ventricular mass index (LVMI) over 12 months.

Findings: In the LC group, pre-dialysis ionised calcium decreased -0.12mmol/L (-0.18-0.06, p=0.0001) and PTH increased 16pmol/L (3.5-28.5, p=0.01) from baseline to 12 months with no significant change in the HC group. In both groups, there was no progression of VC in AA or SFA and no change in PWV, LVMI or BMD. At 12 months, calcimimetics were prescribed in a higher percentage in the LC vs HC groups (45.5% vs 10.5%) with a lower proportion of the HC group being prescribed calcitriol (31.5% vs 72%).

Discussion: Although dialysate calcium prescription influenced biochemical parameters it was not associated with difference in progression of VC between HC and LC groups. An important finding was the potential impact of alternate night NHD in attenuating progression of VC and inducing stabilisation of LVMI and PWV.

Keywords: dialysate calcium concentration, nocturnal hemodialysis, bone mineral metabolism, vascular calcification.

Introduction

There is currently no consensus on the optimal dialysate calcium concentration for patients undertaking varying regimes of hemodialysis (HD). Concerns that calcium loading plays a role in the progression of vascular calcification (VC)[1] contributed to Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommending dialysate calcium concentrations be decreased to maintain a neutral or negative calcium balance[2,3]. This guideline was initially developed with relevance to patients undertaking conventional (3-4 hours, thrice weekly) dialysis. However, when the recommendation of a calcium dialysate of 1.25mmol/L was applied to quotidian nocturnal hemodialysis (NHD) patients, where patients dialysed for six nights per week, it became evident that this approach resulted in a mean net calcium loss manifesting as hyperparathyroidism[4]. Recommendations have since been modified, so for patients undertaking quotidian NHD prescription of an elevated dialysate calcium concentration is suggested[5].

Based on the success of the Canadian NHD programme, enthusiasm for extended hours HD increased, particularly in Australia where a modified programme of alternate night NHD has been widely adopted. Unlike quotidian NHD however, alternate night NHD does not result in as effective control of phosphate, with most patients requiring ongoing prescription of phosphate binder therapy. Despite differences in phosphate control, the prescription of high calcium dialysate was uniformly applied to the alternate night NHD patients in line with recommendations for quotidian NHD. The potential adverse impact of a high calcium dialysate, effectively resulting in an intermittent bolus of calcium with 100% bioavailability delivered over an 8-hour period in a group with frequently inadequately controlled phosphate may be of concern. In addition, there has been little published data on the impact of varying dialysate calcium concentrations on measurable clinical end points, although a recently

published study reported that lower calcium dialysate may slow progression of coronary artery calcification[6]. The few studies that have addressed this issue have generally been small and observational in nature[7-8]. We conducted a randomized controlled trial to compare the effect of low calcium (LC) vs high calcium (HC) dialysate on biochemical and surrogate markers of cardiovascular and bone health in patients undertaking alternate night NHD.

Methods

Study Protocol

We conducted a parallel arm, randomized controlled study where participants were randomly assigned to either HC (1.6mmol/L or 1.75mmol/L depending on site) or LC (1.3mmol/L) dialysate. A computer-generated sequence was adopted for 1:1 randomization with subsequent stratification according to center. The use of sealed opaque envelopes was used for allocation concealment. All patients provided written informed consent to participate in the study. The study protocol was approved by local ethics committees of the two recruiting tertiary referral hospitals in Australia, The Royal Melbourne Hospital (RMH) and Monash Medical Centre (MMC) (*ClinicalTrials.gov registration N^{o}. NCT00395382*).

Study participants

Eligible patients were recruited from RMH and MMC between March 2008 and April 2011. Eligible patients were at least 18 years old and were established on alternate night NHD at home (8 hours, 7 nights per fortnight). Exclusion criteria included being unable or unwilling to follow the study protocol for any reason, non-compliance with HD, scheduled living donor kidney transplant within the next 12 months or participation in another clinical trial.

At the time of recruitment into the study, demographic and co-morbidity data and medication history were recorded. Details on medications specifically recorded included nutritional vitamin D supplementation, calcitriol, phosphate binders, anti-hypertensive agents, cholesterol-lowering statins and cinacalcet. Prescription of all medications was at the discretion of the treating centre. Patients were advised to take cinacalcet in the evening and therefore allowing at least a 10-hour gap between administration of this medication and timing of PTH measurements. Targets for biochemical markers of mineral metabolism were based on local the Caring for Australasians with Renal Impairment (CARI) guidelines at the time, aiming for 2.2-2.6mmol/L for serum calcium (Ca), less than 1.8mmol/L for serum phosphate (Pi) and a parathyroid hormone (PTH) level of 2-3 times the upper limit of normal (CARI 2006).

Dialysis access was via an arteriovenous fistula or arteriovenous graft in all patients. All patients dialysed using machines with polysulphone dialysers of membrane surface area 1.7-2.1m^2. Prescribed blood flow (Qb) was 250mL/min and dialysate flow (Qd) was 500mL/min. Dialysate sodium, bicarbonate, glucose and magnesium concentrations remained constant throughout the study (140mmol/L, 35mmol/L, 5mmol/L and 0.5mmol/L respectively).

Study Outcomes

The primary outcome measurement was the difference in mineral metabolism markers assessed at 0, 3, 6, 9 and 12 months. Secondary endpoints included: (1) progression of VC over a 12-month period as objectively assessed by computed tomography (CT) scans of the abdominal aorta (AA) and superficial femoral arteries (SFAs); (2) change in pulse wave

velocity (PWV); (3) change in left ventricular mass index (LVMI) and valvular calcification over 12 months measured with transthoracic echocardiography (TTE); (4) change in bone mineral density (BMD); (5) change in medications (including active vitamin D and phosphate binder prescription); (6) adverse events, especially episodes of hypercalcemia; and (7) requirement for parathyroidectomy or initiation of cinacalcet.

Laboratory measurements

Blood samples were taken at 3-monthly intervals, immediately prior to and post dialysis. Serum Pi, Ca, bicarbonate and alkaline phosphatase (ALP) were measured using spectrophotometry on a RocheModular D and P Analyser (Roche Diagnostics, Mannheim, Germany). Although the two participating centers analysed samples at their respective laboratories, both centres determined Ca concentration using the same technique of spectrophotometry. Serum Ca was corrected for serum albumin concentration according to the equation [Ca] + 0.02 x (40-[Alb]). Serum ionised Ca was measured using an ion-specific electrode on a standard blood gas analyser (AbacusDiagnostics GEM3000, West Hills, CA, USA). Serum PTH was measured using chemiluminescence acridinium esters on a Nichols Advantage Analyser (Immunodiagnostics, UK). There were no significant delays in blood sampling and measurement in this study.

Computed tomography

CT scans were performed using GE medical systems (UK) Lightspeed 16 multi-slice CT scanner ((120 kVp, 75 mAs and 1.375 pitch). Images were acquired in a spiral mode with the patient lying supine. The scanning range at MMC was from L1 to L4 (infrarenal) and at RMH from T11 to L1 (suprarenal). This allowed visualisation of a greater extent of the abdominal aorta. Images were also acquired of bilateral SFAs. The images were

reconstructed to 10 mm thickness for viewing on the workstation. VC scores were based on the Hounsfield unit (HU) measurement of the aortic wall. HU of any VC in the aorta from both centers were determined by a single radiologist who was blinded to the patient randomization. The number of calcifications and the highest HU of calcifications in the abdominal aorta were recorded.

Trans-thoracic echocardiogram

TTEs were performed using standard echocardiographic equipment (GE HealthcareGmbH, Solingen, Germany) by an experienced consultant in the Cardiac Investigation Units at RMH and MMC. One investigator at each centre reported findings, blinded by patient information and randomization. LVMI was calculated with the Deveruex-modified cube formula[9]. Left ventricular hypertrophy (LVH) was defined as LVMI >55 g/m^2. LV systolic function was assessed visually and ejection fraction (EF) measured using Simpson's biplane method and standard assessment of diastolic function was performed. Valvular calcification for aortic and mitral valves was also recorded using a semi-quantitative scale.

Pulse wave velocity

Arterial stiffness was assessed by tonometry using a SphygmoCor device (AtCor Medical, PWV Inc., Westmead, Sydney, Australia) to measure PWVcf. A pencil-type hand-held probe was used to obtain pulse waveforms at carotid and femoral arterial sites. PWV measures the time interval between pulse waves at the carotid and femoral arteries and higher values represent stiffer vessels. Brachial blood pressure was measured before each PWV determination. A 3-lead electrocardiograph (ECG) was attached to the subject and the surface

distance between pulse points was measured using a tape measure while the patient was supine. All measurements were made by a single operator at each site.

Dual-energy X-ray absorptiometry (DXA)

BMD was assessed by antero-posterior (AP) and lateral DXA scans (GE-Lunar Prodigy; General Electric Medical Services, Australia). Absolute BMD values, Z-scores, and T-scores (number of SD below the BMD of a younger reference group) for lumbar spine (L2 to L4) were reported and mean scores for all subjects were calculated.

Statistical analysis

Given the paucity of published literature, a sample size was difficult to determine. We planned to recruit 50 patients, over the proposed 3-year recruitment period, as this was thought feasible given the NHD populations of both centres involved. Baseline results are expressed as mean +/- SD, median (and range) or frequency (and proportion). Intention-to-treat analyses were performed using random effect linear regression (panel) models to assess for differences between LC and HC groups, with adjustment for baseline differences in the dependent variable. VC models were adjusted for age, duration of end-stage kidney disease (ESKD), diabetes and baseline VC. A P-value of <0.05 was considered to be statistically significant. Intercooled Stata 10.1 (StataCorp, College Station, TX, USA) was used for all statistical analyses.

Results

Patient Characteristics

A total of 65 patients were enrolled and screened, although 15 did not fulfil inclusion criteria (Figure 1). Fifty patients were therefore randomized, with 24 randomized to a LC dialysate and 26 to a HC dialysate. In the LC group, 2 patients withdrew early because of renal transplantation. In the HC group, 6 patients withdrew early (2 transplanted, 2 withdrew consent, 1 developed hypercalcemia and 1 patient was poorly compliant). One patient in the HC group was diagnosed with cancer at 11 months into the study and was included in the intention to treat analysis (22 participants in the LC group and 20 in the HC group). Baseline characteristics of both randomised groups are shown in Table 1. Median ultrafiltration volume, expressed as a percentage (%) of ideal body weight (IBW), was 3% of IBW (IQR: 2.4-4.3%).

Primary outcome

Calcium

At baseline, pre-dialysis corrected serum Ca was similar in both groups. At 6 months, the LC group had lower pre-dialysis serum Ca compared to the HC group. At 9 and 12 months this difference was statistically significant between both groups (Figure 2A). The mean pre-dialysis ionized Ca was not statistically different between the groups at baseline but decreased in the LC group during the study (Table 2) and after 6 months was significantly lower than at baseline in the LC group (Figure 2B). In the HC group there was no change in pre-dialysis ionized Ca throughout the study (Table 2).

Phosphate

Pre-dialysis serum Pi was not statistically different between groups at baseline (Figure 2D). At 6 months Pi was higher in the LC group but at 12 months there was no significant difference between groups.

Parathyroid hormone

At baseline there was no statistically significant difference between the LC and HC groups (Figure 2F). At 12 months, the median PTH in the LC group was statistically higher compared to baseline with an increase in 16 (3.5-28.5) pmol/L (Table 2). The PTH was also significantly higher in the LC group compared to the HC group by 12 months (Figure 2F).

Alkaline phosphatase

Mean ALP levels were not statistically different at baseline, although there was a significant change in the LC group over the 12-month period. In the LC group, mean ALP was 107.6+/-69.1 IU at baseline compared to 146.4+/-80.4 IU at 12 months (p=0.02), whereas mean ALP in the HC group did not significantly change (89.5+-35.8 IU at baseline vs 82.2+/-25.9 IU at 12 months, p=0.31).

25(OH) Vitamin D levels

There were no significant changes in vitamin D levels over the 12 month study period. Levels at baseline were 59.5+/-33.9nmol/L and 65.1+/-31.5nmol/L in the LC and HC groups respectively (p=0.64), with levels at 12 months of 71.8+/-30.6nmol/L and 71.1+/-31.0nmo/L (LC vs HC, p=0.94).

Secondary outcomes

Vascular calcification

At baseline, the median aortic VC score in the LC group was 415 HU (range 0-1188) vs 294 HU (range 0-1158) in the HC group (p=0.25). At 12 months, in the overall cohort, VC was 55 HU lower compared with baseline and there was no difference between the two groups (Figure 3A).

At baseline median right SFA VC was 275 HU (0-1439) in the LC group vs 115 HU (0-625) in the HC group (p=0.12). Median left SFA VC was 225 HU (0-1061) in LC group vs 155 (0-834) in the HC group (p=0.28). At 12 months, there was no significant change in R or L SFA VC compared with baseline, and no significant difference between groups (Figure 3B). The adjusted R SFA VC was 42 HU, 95%CI [-88 – 4.8], lower in the HC vs LC group, p=0.08, and the adjusted L SFA VC was 23 HU, 95%CI [-67 – 19.9], lower in the HC vs LC group, p=0.29.

Left ventricular mass index

At baseline, the mean LVMI in the LC vs HC group was 102.4+/-36.2g/m^2 vs 130+/-26.9g/m^2 (p=0.28). At 12 months, there was no significant progression of LVMI in either group and no difference between groups (Table 3). There was also no difference in valvular calcification (of either the aortic or mitral valves) in either group or over the 12-month period.

Pulse wave velocity

Mean baseline PWVcf in the LC group was 8.1 (5.9-11.1) m/s compared with 6.9 (4.1-10.8) m/s in the HC group (p=0.28). At 12 months, there was no significant increase in PWVcf in either study arm (Table 3).

Bone mineral density

At baseline the lumbar and femoral neck T-scores measured by DXA were similar between groups (Table 3). There were no significant differences in BMD after 12 months.

Medication changes

At baseline 64% of patients in the LC group were prescribed calcitriol which increased to 73% at 12 months (Table 4). In the HC group at baseline, 80% were prescribed calcitriol which reduced to 30% at 12 months. Cinacalcet was prescribed in 18% of LC group with no patients in the HC group being prescribed the medication at baseline. At 12 months, 45.5% of the LC group was prescribed cinacalcet vs 10% of the HC group. One patient in the LC group underwent a parathyroidectomy during the study period. There was no difference in anti-hypertensive medications between groups at baseline or after 12 months.

Adverse events

Table 5 outlines the number of patients in each group with hypocalcemia (<2.20mmol/L) and hypercalcemia (>2.60mmol/L) throughout the study. There were no other significant adverse events during the study period.

Discussion

The choice of dialysate calcium concentration in the management of chronic HD patients can have many important short and long term consequences. During and immediately after dialysis the effects are largely hemodynamic, with longer term consequences relating to impacts on VC and renal osteodystrophy. In a recent randomized controlled study, Ok *et al* reported that lowering dialysate calcium levels slowed the progression of coronary artery calcification (CAC) and improved bone turnover in patients on conventional HD[6]. Apart from

this study, there has however been a paucity of studies assessing effects of varying dialysate calcium concentrations on hard clinical end points such as progression of VC and changes in arterial compliance.

We present a randomized trial to assess the impact of two different dialysate calcium concentrations in patients undertaking alternate night NHD. We report that changes in biochemical parameters of bone and mineral metabolism were significantly different over a 12-month period, predominantly in respect to decreased serum calcium levels and increased PTH levels with patients prescribed LC dialysate. Progression of VC was not seen in either group and there were no significant differences in VC between groups.

NHD has been associated with improved biochemical profiles compared with conventional HD including superior control of phosphate[3,10,11]. There is a risk however in NHD of a negative calcium balance due to minimal use of calcium-based phosphate binders with this risk being greatest with higher rates of ultrafiltration where calcium losses may be significant[4]. Benefits of dialysate with greater calcium concentration have been reported in NHD to prevent calcium depletion and subsequent hyperparathyroidism[3,4,11,12], but there are also concerns from observational studies that higher dialysate calcium concentration may contribute to raised serum calcium levels, greater vascular disease and all-cause mortality[13-14]. In Australia, the commonest schedule is alternate night NHD encompassing seven sessions per fortnight. Despite the reduced frequency of dialysis sessions and the fact that most patients still require phosphate binders, patients undertaking this mode of dialysis have continued to be dialysed with higher calcium baths in line with recommendations for patients on quotidian HD.

It is well established that ESKD is associated with a 10-20 fold increased risk of cardiovascular mortality compared with the general population[15-16]. The availability of increasingly sophisticated non-invasive imaging techniques such as multi-slice CT have confirmed the markedly increased VC burden in patients with ESKD[17-18]. A number of studies have demonstrated a progressive increase in CAC score[19,20,21] after years accumulated on conventional HD. Given the benefits of quotidian NHD on phosphate control and uremia, it has been inferred that this mode of dialysis may be associated with reduced progression of VC. To date, only one small prospective cohort study has reported a non-significant 9% increase in CAC score in patients converting to NHD[22]. In addition to CAC, peripheral vascular calcification and arterial stiffness are highly prevalent in patients on HD and have been identified as independent predictors of all-cause mortality[1]. A study by Sigrist *et al* reported that patients with ESKD and pre-existing VC exhibited significantly increased calcification over 24 months[23]. Whether NHD can ameliorate progression of VC is unclear, with a lack of published evidence. One prospective study of 16 patients on alternate night NHD, where vascular and ectopic calcification was estimated using plain films of the hand and feet at baseline and 12 months, determined that calcification stabilised or improved in 87% of patients[8]. In a case report of a patient on quotidian NHD, there was resolution of iliac and tibial stenosis on Doppler ultrasound despite the use of HC dialysate[24]. In our study, we found no significant change in aortic calcification in either group from baseline to 12 months. Similarly, there was no significant progression of right or left SFA calcification in either group. Although there was no difference in calcification score of the aorta or SFA between the HC and LC dialysate groups, this is the first study showing a potential beneficial effect of alternate night NHD in ameliorating progression of VC.

Calcification of major arteries increases arterial stiffness and PWV which has been shown to be an independent predictor of cardiovascular events in patients with ESKD[25- 26]. Several small studies have reported that PWV increases with duration on conventional HD[14,27]. In addition, there have been a few small series comparing varying dialysate concentrations, suggesting that the use of a HC dialysate results in an increase in PWV, with reduced augmentation index, even after a single dialysis run[28]. The observed effects on PWV after a single dialysis run likely reflect changes in vascular reactivity in response to temporary changes in calcium flux during dialysis. In a more recent retrospective study of patients on conventional thrice weekly HD, the authors found that although there was a slight increase in PWV in all patients over a 6-month period, there was no difference in degree of change between different dialysate calcium concentrations[27]. In our study, there was no significant increase in PWVcf from baseline to 12 months in either group. These results provide further evidence that extended hours HD may ameliorate the development of increased arterial stiffness, so frequently observed in patients on conventional HD.

LVH is common in patients on dialysis and is an independent predictor of cardiovascular morbidity and mortality[29,30]. Unfortunately, progression of LVH is common in patients on conventional HD but in a randomized controlled trial, Culleton *et al* demonstrated improved LV mass in patients with quotidian NHD[31]. In our study, there was no significant progression of LVH in patients in either group over 12 months and the number of antihypertensive agents prescribed was low throughout the study. We believe this is the first study demonstrating the effectiveness of alternate night NHD in stabilisation of LVMI over this time period. In addition to stabilisation of LVMI, there was no evidence of progressive valvular calcification as determined by echocardiography.

Randomization to HC vs LC dialysate had a significant effect on markers of bone mineral metabolism with the HC group demonstrating higher pre-dialysis ionised calcium levels and significantly lower PTH levels than the LC group. These biochemical changes affected prescription of calcitriol and cinacalcet throughout the study period. In the HC dialysate arm, there was a reduction in the prescription of calcitriol, with only 30% on this medication at 12 months compared with 80% at baseline. There was also a reduction in the use of calcium-based phosphate binders in the HC dialysate group perhaps related to concerns about potential hypercalcemia. Conversely in the LC dialysate group, although there were more patients on calcitriol at study end compared with baseline (73% vs 64%), there was a greater percentage of these patients prescribed cinacalcet at 12 months compared with the HC arm (45.5% vs 10%), possibly to manage the progressive hyperparathyroidism.

In summary, we did not show a difference in progression of vascular disease between subjects dialysed with a low vs high calcium concentrations, although an important and novel finding of our study was the lack of progression of VC and the stabilisation of LVMI and PWVcf over a 12-month period in this cohort of patients on alternate night NHD. This outcome is in contrast to the reported rates of progression of calcification and LVH reported in patients on conventional thrice weekly HD[23,19,20,32]. Limitations of this study include small sample size, lack of data on residual renal function, and the end-points being surrogate markers of bone and mineral disease and cardiovascular health.

Acknowledgements: This study was supported by an educational grant from Roche Pharmaceuticals

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Legends to figures

Figure 1. Flow of study participants.

Figure 2. Change in biochemical parameters over 12 months comparing low vs high dialysate calcium groups: (A) pre-dialysis corrected calcium, (B) pre-dialysis ionised calcium, (C) post-dialysis calcium, (D) pre-dialysis phosphate, (E) post-dialysis phosphate, and (F) PTH. (* $p<0.05$ ** $p<0.01$ *** $p<0.001$ vs LC group at baseline)

Figure 3. Change in vascular calcification over 12 months comparing differences between low vs high calcium dialysate groups: (A) aorta, and (B) right and left superficial femoral arteries.

Tables

Table 1. Baseline demographics of study participants comparing low calcium (LC) and high calcium (HC) dialysate

	LC group n=22	HC group n=21	P-value
Age, yrs median (IQR)	54.5 (39-65)	47 (41-55)	0.39
Gender M:F	15:7	16:5	0.73
ESKD, mths median (IQR)	61 (18-85)	40 (18-119)	0.57
Dialysis, mths median (IQR)	25.5 (6-42)	15 (5-27)	0.67
Diabetes n (%)	3 (14)	4 (18)	0.70
IHD n (%)	5 (23)	5 (24)	1.00
Cause of ESKD n (%)			0.62
GN	8 (36)	7 (33)	
HT	0 (0)	1 (5)	
Diabetes	1 (5)	2 (10)	
PCKD	1 (5)	2 (10)	
Other	10 (45)	6 (29)	

Abbreviations: ESKD, end-stage kidney disease; GN, glomerulonephritis; HT, hypertension; IHD, ischemic heart disease; IQR, interquartile range; PCKD, polycystic kidney disease

Table 2. Change in serum biochemical markers of mineral metabolism in each group by 12 months

	LC group	P value	HC group	P value
Pre-dialysis Ca (mmol/L)	-0.18 (-0.26 - -0.09)	<0.0001	-0.01 (-0.12 - 0.09)	0.78
Post-dialysis Ca (mmol/L)	-0.17 (-0.28 - -0.06)	0.002	0.17 (0.02 - 0.31)	0.02
Ionised Ca (mmol/L)	-0.12 (-0.18 - -0.06)	<0.0001	-0.01(-0.75 - 0.06)	0.83
Pre-dialysis Pi (mmol/L)	-0.04 (-0.24 - -0.16)	0.673	-0.15 (-0.46 - 0.15)	0.31
Post-dialysis Pi (mmol/L)	-0.01 (0.18 - 0.15)	0.903	0.02 (-1.72 - 0.21)	0.83
PTH (nmol/L)	16.0 (3.5 - 28.5)	0.012	5.03 (-12.1 - 22.2)	0.57

Mean differences with 95% CI

Abbreviations: Ca, calcium; Pi, phosphate, PTH, parathyroid hormone; LC, low calcium; HC, high calcium

Table 3. Change in secondary outcome measures from baseline to 12 months

	LC group	HC group	P value (LC vs HC)
PWV- baseline	8.1 +/-1.9	7.6 +/-1.7	0.28
PWV- 12 months	7.1 +/-1.5	8.4 +/-2.1	
p value (change over 12mths)	0.26	0.34	
Lumbar spine BMD- baseline	-0.73 +/- 1.61	-0.98 +/- 1.75	0.69
Lumbar spine BMD- 12 months	-0.53 +/- 1.63	-0.72 +/- 1.63	0.64
p value (change over 12mths)	0.05	0.79	
Femoral neck BMD- baseline	-1.41 +/- 1.25	-1.32 +/- 1.34	0.64
Femoral neck BMD- 12 months	-1.12 +/- 0.88	-1.11 +/- 0.92	0.86
p value (change over 12mths)	0.58	0.88	
LVMI- baseline	102.4 +/- 36.2	130.5 +/- 26.9	0.28
LVMI- 12 months	106.6 +/- 21.9	123.2 +/- 34.2	0.12
p value (change over 12mths)	0.60	0.40	

Abbreviations: BMD, bone mineral density; LVMI, left ventricular mass index; PWV, pulse wave velocity; LC, low calcium; HC, high calcium

Table 4. Change in medication prescription over the 12-month study period

	Baseline		12 Months		
	LC	**HC**	**LC**	**HC**	**P value**
All phosphate binders	14	12	13	6	0.06
Calcium-based binders	8	9	8	2	0.07
Non-calcium binders	7	6	6	4	0.72
Calcitriol *	14	16	16	6	0.006
Cinacalcet #	4	0	10	2	0.016
Anti-hypertensive agents	9	11	8	9	0.83

*Calcitriol dose (mean +/- SD, ug/week): LC vs HC, 1.3±1.6 vs 1.5±1.4 for baseline; 1.8±3.3 vs 0.36±0.6 at 12 months

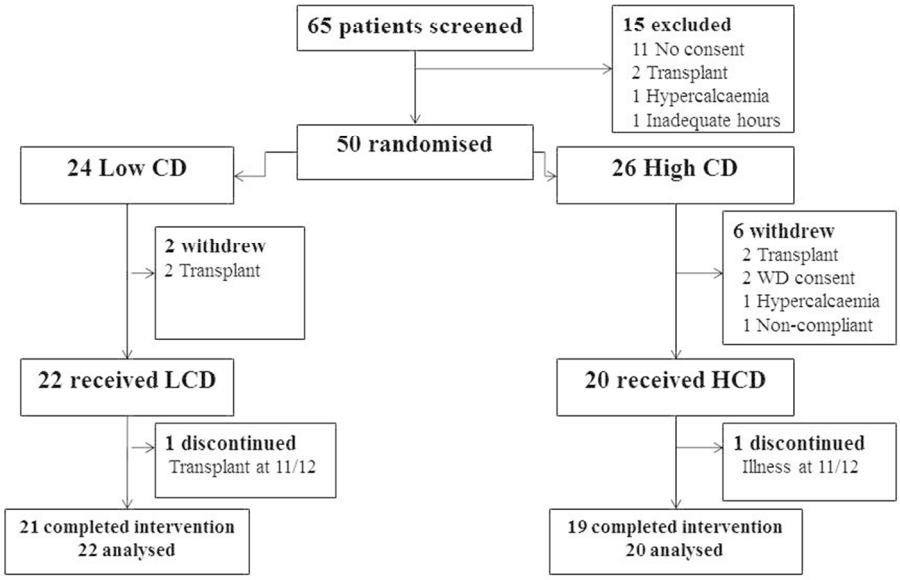
#Cinacalcet dose (mg/week): LC vs HC, 54±91 vs 0 for baseline; 141±216 vs 29±100 at 12 months

Abbreviations: LC, low calcium; HC, high calcium

Table 5. Number of patients with abnormal serum calcium levels (mmol/L) throughout the study

	LC group		HC group	
	Ca<2.20	**Ca >2.60**	**Ca <2.20**	**Ca >2.60**
Baseline	3	4	2	1
3 Months	1	2	1	1
12 Months	9	1	1	1

Abbreviations: Ca, calcium; LC, low calcium; HC, high calcium



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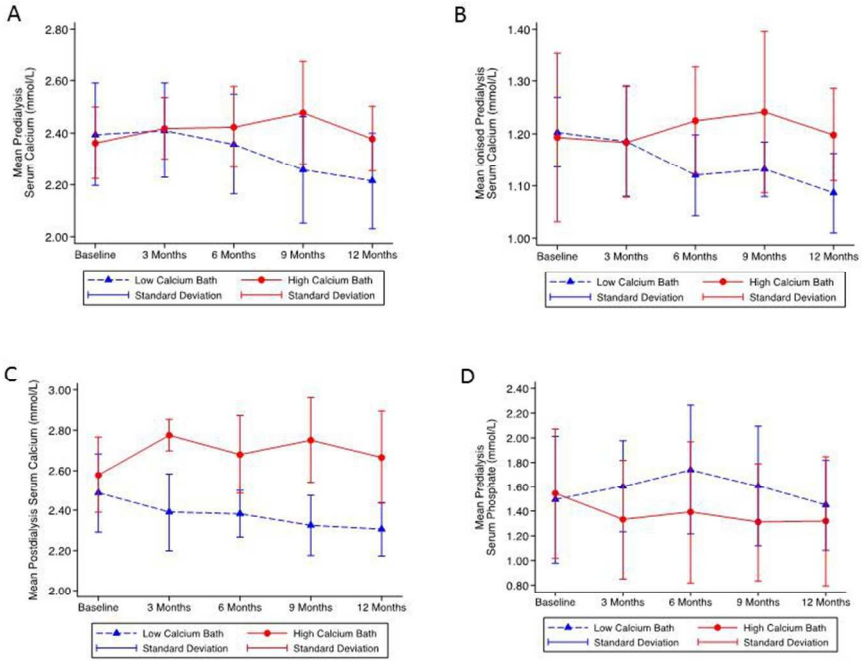

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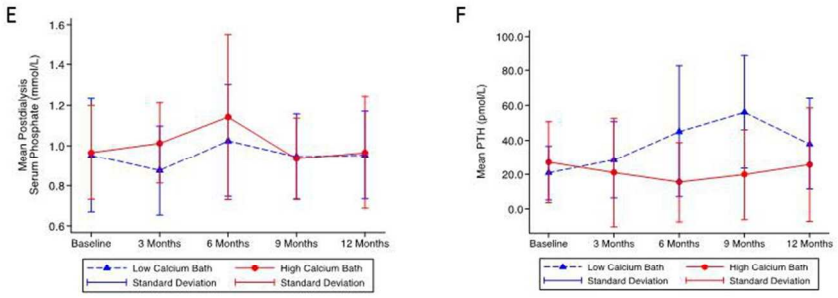

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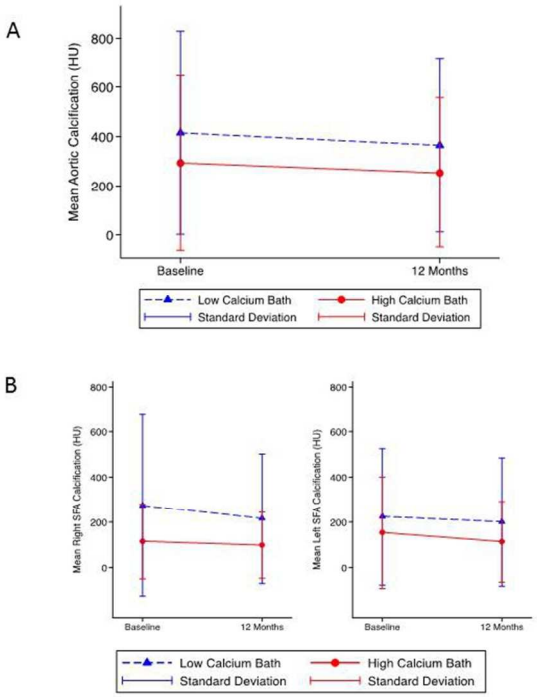

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Author/s:
Masterson, R;Blair, S;Polkinghorne, KR;Lau, KK;Lian, M;Strauss, BJ;Morgan, JG;Kerr, P;Toussaint, ND

Title:
Low versus high dialysate calcium concentration in alternate night nocturnal hemodialysis: A randomized controlled trial

Date:
2017-01-01

Citation:
Masterson, R., Blair, S., Polkinghorne, K. R., Lau, K. K., Lian, M., Strauss, B. J., Morgan, J. G., Kerr, P. & Toussaint, N. D. (2017). Low versus high dialysate calcium concentration in alternate night nocturnal hemodialysis: A randomized controlled trial. HEMODIALYSIS INTERNATIONAL, 21 (1), pp.19-28. https://doi.org/10.1111/hdi.12452.