
Trainee Forum

Review of dialysate calcium concentration in hemodialysis

Nigel TOUSSAINT, Patrick COONEY, Peter G. KERR

Department of Nephrology, Monash Medical Centre, Clayton, Vic., Australia

Abstract

The dialysate calcium (Ca) concentration for hemodialysis (HD) patients can be adjusted to manage more optimally the body's Ca and phosphate balance, and thus improve bone metabolism as well as reduce accelerated arteriosclerosis and cardiovascular mortality. The appropriate dialysate Ca concentration allowing this balance should be prescribed to each individual patient depending on a multitude of variable factors relating to Ca load. A lower dialysate Ca concentration of 1.25 to 1.3 mmol/L will permit the use of vitamin D supplements and Ca-based phosphate binders in clinical practice, with much less risk of Ca loading and resultant hypercalcemia and calcification. Low Ca baths are useful in the setting of adynamic bone disease where an increase in bone turnover is required. However, low Ca levels in the dialysate may also predispose to cardiac arrhythmias and hemodynamically unstable dialysis sessions with intradialytic hypotension. Higher Ca dialysate is useful to sustain normal serum Ca levels where patients are not taking Ca-based binders or if Ca supplements are not able to normalize serum levels. Suppression of hyperparathyroidism is also effective with dialysate Ca of 1.75 mmol/L, but hypercalcemia, metastatic calcification, and over-suppression of parathyroid hormone are risks. Dialysate Ca of 1.5 mmol/L may be a compromise between bone protection and reduction in cardiovascular risk for conventional HD and is a common concentration used throughout the world. The increase in longer, more frequent dialysis such as short-daily and nocturnal HD, however, provides another challenge with regard to optimal dialysate Ca levels and higher levels of 1.75 mmol/L are probably indicated in this setting. Difficulties in determining the ideal dialysate Ca occur because of the complex pathophysiology of bone and mineral metabolism in HD patients and there needs to be a balance between dialysis prescription and other treatment modalities. To optimize management of the abnormal Ca balance, other aspects of this disorder need to be more fully clarified and, with evolving medications for phosphate control and treatment of secondary hyperparathyroidism, as well as the emergence of a multitude of different HD regimes, further studies are required to make definitive recommendations. At present, we need to maintain flexibility with HD treatments and so dialysate Ca needs to be individualized to meet the specific requirements of patients by optimizing management of renal bone disease and simultaneously reducing metastatic calcification and cardiovascular disease.

Key words: Dialysate calcium, hemodialysis, calcium balance, vascular calcification, mineral metabolism, calcium × phosphate product

Correspondence to: P. G. Kerr, Department of Nephrology, Monash Medical Centre, 246 Clayton Rd, Clayton, Vic. 3168, Australia.

E-mail: peter.kerr@med.monash.edu.au

CLINICAL TRAINING AT MONASH MEDICAL CENTRE, CLAYTON, MELBOURNE, VIC., AUSTRALIA

The training pathway for medical specialties in Australia is governed by the Royal Australasian College of Physicians (covering Australia and New Zealand). After a compulsory intern year, trainees typically enter “basic training” that incorporates exposure to all medical specialties and general medicine. This occurs predominantly in teaching hospitals with some secondment to smaller suburban and rural hospitals. Basic training takes 3 years, wherein trainees progress through working as a resident doctor (similar to a House Officer) to registrar level where they supervise residents. In the third year of this training, there are 2 examinations. Firstly, there is the written exam (multiple choice format), which incorporates clinical sciences and clinical medicine in all internal medical disciplines. If successful at this examination, candidates may then sit a clinical examination, which has a format of long and short cases extending over a whole day (2 long cases and 4 short cases)—again, cases are drawn from all aspects of internal medicine.

Once successful at the examinations, candidates complete the 3 years of basic training and enter “advanced training.” This is usually discipline specific—in the case in point, in nephrology. Advanced training spans a further 3 years and incorporates at least 2 clinical years as a Nephrology Registrar but may include a third elective year, either in another specialty or in research. Many candidates overlap a PhD year at this point. There are no exit examinations but there are annual reports on progress, submitted to a Specialist Advisory Committee that is discipline specific.

At Monash Medical Centre, we run a large program by Australian standards. The Nephrology Department cares for 485 dialysis patients and over 500 transplant patients, including kidney–pancreas transplantation. There are 3 clinical registrars who rotate through care of the inpatient ward, dialysis, and transplantation (transplant patients are cared for by the Physicians in Australia). There are usually about 25 to 30 inpatients at any one time but renal biopsies and many surgical procedures are performed as day cases. We perform around 300 renal biopsies per year (native and transplant), and there are about 40 to 45 transplants per year (including 8–10 kidney-pancreas).

Educational activities include formal rounding with the consultant 3 times/week, separately in general nephrology and transplantation, and attendance at a dialysis clinic weekly and a glomerulonephritis clinic weekly. There are 2 formal transplant clinics weekly, plus daily

drop-in clinics. All clinics are followed by a discussion of the patients seen, with all attendees at the clinic (consultants, registrars, and residents)—this usually takes up to an hour. There is a weekly department meeting with presentations of renal histology, scientific work, or other nephrology topics and there is a second weekly journal club. The hospital has a weekly general medicine meeting as well (similar to a grand round). In addition, all advanced trainees must complete a “project” in each year of training—this is usually a small clinical research topic, many of which have been published.

The department also has 5 nephrology PhD students who have completed their advanced training but who have elected to pursue research. Three are involved in laboratory research (glomerulonephritis, diabetes, and peritoneal membrane pathobiology) and 2 in clinical research (dialysis nutrition and vascular disease). The Department is currently involved in 23 clinical trials and has an active basic science laboratory, including 14 scientists.

Training in dialysis

As mentioned, Monash Medical Centre cares for about 485 dialysis patients, including 135 patients on peritoneal dialysis (PD), and there are about 70 to 90 new dialysis patients entering the program each year. Dialysis education for advanced trainees occurs at a variety of levels, including treating in-hospital patients and ambulatory care patients. Peritoneal dialysis is offered as CAPD and APD; hemodialysis (HD) is offered as satellite and home (in-center tends to be a transit zone only). Home HD includes conventional and nocturnal dialysis, and the department currently has 31 patients on nocturnal HD.

The registrar covering dialysis at any one time is responsible for ambulatory management of outpatient HD and PD patients. As with all nephrology units in Melbourne, training in ambulatory dialysis for the advanced trainee at Monash Medical Centre occurs throughout the duration of the 3 years of clinical practice as a registrar, and is integral to the overall efficiency of HD patient care in the department. There is one co-ordinated dialysis outpatient clinic per week with regular attendance by Consultants and registrars, as well as allied health staff including a dietician, social worker, and dialysis educators.

There are 20 to 25 HD inpatients at any one time cared for by the ward registrar, but with good clinical practice most management of patients will occur in the community with regular out-patient review. In-patient HD training involves regular ward rounds with the consultant, and direct communication with dialysis nursing staff and between registrars. There would typically be about

10 to 15 acute HD patient admissions per month, and review of patients in the intensive care setting, especially of those requiring support with hemofiltration, is also crucial to optimal training of advanced trainees at Monash Medical Centre.

DIALYSATE CALCIUM

Clinical scenerio

A 54-year-old male has been managed with HD for 3 years. His dialysis parameters include—4 hr, 3 times/week, using a 1.6 m² polysulfone high-flux dialyzer, achieving a spKt/V of 1.5. He has always struggled with phosphate control. Owing to regulatory restrictions, sevelamar hydrochloride is unavailable. His phosphate control includes calcium carbonate, 2 tablets 3 times daily with meals, and aluminum hydroxide, 1 tablet 3 times daily with meals. He also takes calcitriol 0.25 mcg daily. His serum calcium is 2.6 mmol/L, phosphate 2.1 mmol/L, intact parathyroid hormone (iPTH) level is 53 pmol/L, and albumin is 38 g/L. One is concerned about his iPTH level and would like to increase his calcium carbonate to 9 tablets daily but are concerned about his serum calcium.

What options in the dialysate calcium concentration are available? What is the “correct” dialysate calcium?

REVIEW

Introduction

Using the appropriate dialysate calcium (Ca) concentration in HD patients has important management implications with regard to the prevention of renal bone disease and also, more importantly, the reduction of vascular calcification. Manipulations of the dialysate Ca concentration enable alterations in Ca load as dialysate Ca impacts on serum Ca, phosphate, and parathyroid hormone (PTH) and, most likely, soft tissue calcification. Concentrations in the dialysate can be customized depending on the current and targeted serum Ca levels as well as the desire to maintain hemodynamic stability during dialysis.¹

Historical perspective

Dialysate in general, with its electrolyte and acid-base components, has evolved specifically and scientifically through studies to provide the best outcome measures for patients on HD, but the optimal dialysate Ca concentration is yet to be delineated.² When dialysis was initially introduced in the 1960s, 1.25 mmol/L dialysate Ca con-

centration was used as this most closely matched normal serum ionized Ca. It was soon discovered that higher levels of Ca were required to sustain serum Ca levels and to increase Ca load, therefore preventing hypocalcemia and renal bone disease.³

The administration of active vitamin D (calcitriol) in the 1970s eliminated the need for the dialysate to improve Ca load and a higher dialysate Ca concentration, with a net flux of Ca into the patient, was not required. With the introduction of Ca-based phosphate binders in the late 1980s, in association with calcitriol use, hypercalcemia became a more common potential problem, and a lower Ca dialysate was re-introduced. Slatapolsky et al., in 1986, reported on HD patients receiving Ca carbonate as phosphate binders in association with dialysis containing 1.75 mmol/L Ca dialysate revealing the complication of hypercalcemia.⁴ A repeat analysis of patients reported in 1989, with lower Ca dialysate (1.25 mmol/L) and associated Ca carbonate administration, at an average dose of 10.5 g/day, demonstrated no hypercalcemia.⁵ The benefits of low Ca dialysate in association with Ca-containing binders and also with calcitriol have also been confirmed in many early studies, with the active vitamin D component effective in treating patients with secondary hyperparathyroidism (HPT).^{6,7}

However, the more recent introduction of non-Ca, nonaluminum-based phosphate binders, noncalcemic vitamin D analogues, as well as the emergence of calcimimetic agents into clinical practice improving management of mineral metabolism, have made the current choice of dialysate Ca even more difficult, and also more crucial.

Current management of mineral metabolism

Patients with end-stage kidney disease (ESKD) have a disruption in systemic Ca and phosphate homeostasis. As a result of limited excretion of phosphate, diminished hydroxylation of 25-hydroxyvitamin D to calcitriol (1,25-dihydroxyvitamin D) and resulting hypocalcemia, there is an effect on bone, the gut, and the parathyroid glands. Hypersecretion of PTH is initially appropriate by increasing Ca phosphate release from bone and enhancing urinary phosphate excretion (via a decrease in proximal reabsorption). PTH can, in early stages, correct both the hypocalcemia and the hyperphosphatemia. With declining kidney function, worsening phosphate retention is intimately related to the common development of secondary HPT. The latter is a major cause for concern because the high circulating levels of PTH play an important role in the development of renal osteodystrophy and pos-

sibly in other uremic complications as well. Increased levels of PTH are also closely associated with cardiovascular disease in dialysis patients.

Current management of mineral metabolism in ESKD involves the control of hyperphosphatemia and the use of active vitamin D compounds to suppress PTH, with an aim to obtain normalization of serum Ca and phosphate. Phosphate control in dialysis patients is difficult and management relies on dietary restriction, the use of phosphate binders, many of which are Ca-based, and dialysis.⁸ Dialysis has limited ability for phosphate control although phosphate removal by HD is very much a time-dependent process.⁹

Aluminum hydroxide was initially thought to be the ideal phosphate binder, especially being the most cost effective; however, it has largely been abandoned because of the risks of aluminum toxicity with osteomalacia and encephalopathy.¹⁰ If aluminum-based binders are needed, certain guidelines recommend against their use for longer than 4 weeks.² Ca carbonate and Ca acetate subsequently replaced aluminum hydroxide as the most commonly used phosphate binders but their use is associated with hypercalcemia, especially in association with the use of vitamin D metabolites or higher dialysate Ca concentrations.¹¹ Although patients were previously dialyzed against 1.5 or 1.75 mmol/L Ca baths to prevent Ca depletion, as mentioned with the widespread use of Ca-salts, as phosphate binders, reduced Ca dialysate became standard. More physiological dialysate with a lower Ca of 1.25 mmol/L allowed for increased intestinal Ca absorption with Ca-based medication, without a positive dialysis Ca balance and resultant hypercalcemia.^{12,13}

With this change, however, there is an association with worsening secondary HPT, as a result of negative dialysis Ca balances, and the use of Ca-containing binders is perhaps only more likely to accelerate the process of Ca deposition and vascular calcification.^{12,14–17} Also, a lower dialysate Ca has not been shown to produce positive effects in a study of health-related quality-of-life parameters.¹⁷

The more recent introduction of Ca-free binders, with a decrease in the overall intestinal Ca absorption, now alters the balance toward an overall negative Ca load with the potential to stimulate PTH production. Therefore, a trend toward the use of higher concentrations of dialysate Ca has been recommended to avoid Ca depletion and 1.5 mmol/L Ca bath has subsequently become more accepted for the majority of HD patients. This level seems to be suitable because the moderately negative dialysis balances can be easily counterbalanced by the administration of mild doses of Ca-containing binders, if necessary, in order to ensure a neutral total body Ca balance.¹⁸

Worldwide practice

Worldwide use of dialysate Ca varies throughout different countries. The most recent clinical practice guidelines by the National Kidney Foundation (New York, United States) Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines recommend a dialysate Ca concentration of 1.25 mmol/L rather than 1.5 mmol/L to avoid excess Ca load and prevent vascular calcification,² whereas in Japan and Australia a dialysate of 1.5 mmol/L is common. There is no recommendation for dialysate Ca in the European Best Practice Guidelines (EBPG). The first Dialysis Outcomes and Practice Patterns Study (DOPPS) involved 307 HD centers with participants from Japan, United States, and Europe, and revealed that the average dialysate Ca concentration was 1.45 mmol/L, 60% of patients exceeding the K/DOQI recommendation.¹⁹ Lower dialysate Ca in general was more predominantly used in the United States. Interestingly, from the DOPPS data there was a significantly increased all-cause (but not cardiovascular) mortality risk associated with a higher Ca dialysate.

Despite all studies so far, recommendations worldwide are based mostly on opinion, with mortality and morbidity data currently lacking, to answer the question of which dialysate Ca is the safest and most effective. Recommendations from Locatelli et al., based on a consensus from the third "Accord Workshop," held in Paris in 2000 and published in 2002, suggested that the dialysate Ca content should be 1.5 to 1.75 mmol/L, with 1.5 mmol/L preferred in patients taking Ca supplements or vitamin D analogues to avoid a positive Ca balance.²⁰ The consensus recommended a dialysate Ca concentration of 1.75 mmol/L if patients were not on these medications, and it suggested that 1.25 mmol/L should be avoided for prolonged periods due to risks of aggravating secondary HPT.

Given the interplay between dialysate Ca concentrations and medication administration with regard to serum Ca and phosphate control, changes in the practice of phosphate binder prescription are important in providing the optimal Ca dialysate concentration. More than 80% of all dialysis patients are managed with phosphate binders, Ca-based agents previously being the most predominant worldwide,¹⁹ however, the most recent DOPPS data (2002–2004) revealed that 25.9% of patients were taking the Ca-free binder sevelamer, compared with 0.1% of patients using sevelamer during the initial observation period (1996–2001).²¹ Phosphate binder usage differs across countries, with currently over half of patients in the United States and some Western European countries being managed with non-Ca-based binders, although Ca

acetate may still be more cost effective.¹⁰ In some countries, non-Ca-based phosphate binders such as sevelamer and lanthanum are not readily available due to regulatory and cost issues.

Dialysis Ca physiology

The diffusion of Ca in HD depends on the Ca gradient between the serum concentration and the dialysate concentration. Studies have shown that when the dialysate Ca is greater than 1.5 mmol/L, there is an expected gain in Ca.^{11,22,23} Losses by convective transport, however, can exceed the amount of Ca gained by diffusion²² so ultrafiltration is also an important factor in the overall Ca balance. Ca mass balance studies have demonstrated that generally, providing the patient is normocalcemic, a dialysate Ca concentration of 1.75 mmol/L produces a positive Ca balance and a negative balance is obtained with a dialysate Ca of 1.25 mmol/L.^{23–25} Dialysate free of Ca has been shown in one early human study to produce symptomatic hypocalcemia within the first 60 min of dialysis for chronic HD patients²⁶ and hypotension can also result from inadvertent use of a Ca-free dialysate.²⁷

Ca ions are extremely important in the contractile process of both vascular smooth muscle cells and cardiac myocytes and changes can have significant effects on hemodynamics.²⁸ Whether this effect is a result of changes in myocardial contractility or mediated through vascular reactivity is unclear. Serum ionized Ca increases during sessions with dialysate Ca of 1.5 and 1.75 mmol/L and decreases to the lower limits of normal after HD with 1.25 mmol/L. Van Kuijk et al., reported that with the lower dialysate Ca concentration, there is a significantly larger decline in blood pressure compared with higher dialysate Ca in patients with normal cardiac function.²⁹ This is perhaps related to decreased left ventricular contractility using the lower dialysate Ca. Stable blood pressure is also achieved with the use of higher dialysate Ca in those patients with impaired cardiac function.³⁰

HD with a dialysate Ca bath of 1.75 mmol/L therefore seems to be a possible strategy for improving hemodynamic stability in patients, especially for those with cardiac impairment.³¹ This therapy, however, is limited by the concerns of developing hypercalcemia with resultant excessive Ca loads exacerbating vascular calcification. The recent introduction of calcimimetics, as well as the widespread use of Ca-free phosphate binders, may provide the opportunity to use a higher dialysate Ca concentration without the effect of predisposing cardiovascular mortality (Table 1).

Cardiovascular morbidity and vascular calcification

The leading cause of mortality in patients with ESKD is cardiovascular disease.^{32,33} Compared with the general population, dialysis patients have a 3- to 30-fold increase in mortality, depending on the age group examined.³³ This excess in mortality compared with the general population is not explained by the presence of traditional cardiovascular risk factors, and a large component of the vascular calcification is likely due to the chemical problem of Ca and phosphate excess. Precipitation of Ca and phosphate may be responsible for much of the medial arterial calcification and the Ca \times phosphate product (Ca \times P) is an independent risk factor for vascular calcification and cardiovascular death.³⁴ It has also been demonstrated that phosphate levels are linearly and independently associated with all-cause and cardiovascular mortality in dialysis and predialysis patients.³⁴

Vascular calcification is not, however, as simple as “Ca loading” with passive precipitation of Ca and phosphate when one or more of these minerals are in excess. It is now recognized that this extra-osseous calcification in ESKD is an active process involving vascular smooth muscle cell transformation to osteoblast-like cells with elevated phosphate levels and other as yet unidentified uremic toxins inducing this differentiation. Only once mineralization is initiated will alterations in Ca and phosphate balance accelerate this process via multiple mechanisms.^{35–37} In recent years, several mechanisms have been identified to explain vascular calcification including loss of inhibition, induction of bone formation, circulating nucleation complexes, and cell death. An elevated Ca \times P combination is likely to be a predominant risk factor and Ca alone may also be problematic because, in general, a positive Ca balance may promote or accelerate soft-tissue and vascular calcification even in the absence of hypercalcemia.³⁸ During conventional HD, a positive Ca balance and a concomitant inflammatory state probably act as co-factors in the development of calcifications.³⁹

Studies using electron-beam computed tomography (EBCT) have accurately and quantitatively assessed coronary artery calcification with total calcification scores proven to be strongly predictive of coronary artery atherosclerosis and of major future adverse cardiac events in the general population.^{40,41} In those patients with ESKD, calcification scores are also markedly increased, especially at a younger age, and progress more rapidly, although the prognostic significance of EBCT in this population has only recently been investigated.^{16,42–45}

The presence and extent of vascular calcification in ESKD is consistently linked to an increased risk of death. Modalities for determining the degree of calcification, including plain radiography,⁴⁵ ultrasound,⁴⁶ and EBCT,⁴⁴ have all correlated greater calcification with poorer prognosis and shown that vascular calcification is a strong and independent predictor of cardiovascular and all-cause mortality in HD patients. The administration of Ca-containing phosphate binders is associated with progressive coronary calcification but correlation between dialysate Ca levels and EBCT is yet to be determined.

Hemodynamic stability on dialysis

Serum-ionized Ca levels are a determinant of vasoconstriction; therefore, alterations in dialysate Ca concentration may impact on arterial compliance. One study looking at the effect of treatment with lower dialysate Ca revealed favorable changes in blood pressure and arterial compliance as well as a reduction in serum aldosterone levels (a marker of vasoactivity).⁴⁷ However, cardiac arrhythmias are also more likely to occur in HD patients with lower dialysate Ca associated with the potential for worsening of QT prolongation.^{48,49}

Intradialytic hypotension remains a problem in HD and the etiology is multifactorial. As outlined earlier, one predisposition has been low dialysate Ca and one study, where HD patients underwent alternate dialysis with 1.25 and 1.75 mmol/L dialysate Ca, revealed a minor but statistically significant reduction in mean blood pressure with the use of the lower Ca bath.⁵⁰ Manipulations have shown to improve efficacy with this regard by using higher Ca dialysate.^{51,52} More hemodynamically stable dialysis sessions, without intradialytic hypotension, may be achieved with a dialysate Ca of 1.75 mmol/L and result in subsequent improved morbidity. For patients with cardiac impairment and reduced life-span, the benefits of reduction in dialysis events could be weighed against the potential long-term effects of a higher dialysate Ca concentration with increases in vascular calcification that may not affect life expectancy. Increasing the magnesium dialysate concentration to 0.75 mmol/L may also be of benefit for a lower (1.25 mmol/L) dialysate Ca to reduce the incidence of intradialytic hypotension.⁵³

Blood pressure may be altered by changes in Ca either through alterations in systemic vascular resistance or changes in cardiac output, or both. A study of 8 HD patients with variable dialysate Ca from 0.5 to 2.5 mmol/L showed changes in blood pressure with alterations in Ca levels.⁵⁴ Higher Ca dialysate augmented cardiac output while leaving vascular resistance unchanged, so it was con-

cluded that the effect of serum Ca on blood pressure was through left ventricular (LV) stroke volume and output.

It has been postulated that an increase in serum-ionized Ca during HD could also potentially lead to impaired LV relaxation. However, using a dialysate Ca concentration of 1.75 mmol/L one study showed that perhaps this was not necessarily the case, revealing no change in Doppler measures of LV diastolic function with an increase in serum Ca after 1 hr of HD without ultrafiltration.⁵⁵ Instead, changes in these LV parameters were thought more likely to be related to preload.

Renal bone disease

All patients with ESKD will have renal bone disease by the time they require dialysis. On dialysis, this does not improve but progresses and in HD patients renal bone disease is a serious complication that can result in fractures, bone pain, and extraosseous calcification. Several different factors contribute to bone disease and a spectrum exists from high bone turnover disease, related to secondary HPT, to low bone turnover disease due to osteomalacia or adynamic bone disease, the latter a result of aluminum toxicity or more commonly overtreatment of HPT with vitamin D.

Clinically, the distinction between these pathological diagnoses is often based on the serum PTH level. Parathyroid hormone levels of less than 11 pmol/L (100 pg/mL) are suggestive of adynamic bone disease and levels greater than 33 pmol/L (300 pg/mL) are indicative of overstimulating PTH and high turnover bone disease. Dialysate Ca has been shown to consistently correlate inversely with PTH and therefore higher Ca dialysate will suppress HPT and lower Ca levels will improve turnover and increase PTH.

The diagnostic value of serum PTH levels to predict accurately the nature of renal bone disease, however, is debatable. Levels between 11 pmol/L (100 pg/ml) and 55 pmol/L (500 pg/ml) are probably insufficiently sensitive or specific to diagnose either low or high turnover bone disease.² The K/DOQI guidelines suggest that if a patient with ESKD and serum levels of intact PTH between 11 and 55 pmol/L develops unexplained hypercalcemia, bone pain, or an increase in bone alkaline phosphatase (ALP) activity, a bone biopsy can be useful. The bone biopsy will allow more accurate assessment of the rate of bone formation and bone mineralization and will help guide therapy.²

For patients with adynamic bone disease (low or low-normal bone turnover), the use of lower dialysate may be beneficial. These patients are at a higher risk of cardiovascular mortality and often have high Ca \times P as a result

Table 1 Potential advantages and disadvantages of different dialysate calcium concentrations

| Dialysate calcium | Advantages | Disadvantages |
|--------------------------|---|---|
| Lower (1.25–1.5 mmol/L) | Reduces risk of hypercalcemia Allows greater use of vitamin D and calcium-containing phosphate binders Benefit in adynamic bone disease | Potential for negative calcium balance and stimulation of PTH Increase in intra-dialytic hypotension |
| Higher (1.5–1.75 mmol/L) | Improves hemodynamic stability Suppression of PTH Beneficial for bone protection in nocturnal hemodialysis | Greater risk of hypercalcemia Limits use of vitamin D and calcium based binders Possible risk of vascular calcification |

PTH=parathyroid hormone.

of high serum Ca levels.⁵⁶ In one prospective study of HD patients with biochemical markers suggestive of adynamic bone disease, dialysate Ca was reduced from 1.75 to 1.25 mmol/L in patients to assess bone metabolism.⁵⁷ This demonstrated a significant reduction in $\text{Ca} \times \text{P}$ (5.62–3.95) and an increase in PTH. Parameters of bone resorption (pyridinoline) and formation (bone ALP) were significantly increased, peaking after 12 months. Treatment with a lower dialysate Ca may therefore be potentially advantageous in this clinical setting to stimulate bone turnover.

Another study reviewing 67 patients, with the dialysate Ca reduced from 1.5 to 1.25 mmol/L, also analyzed bone metabolism and revealed an initial increase in PTH and osteocalcin.⁵⁸ In a subgroup with initially low PTH levels (<11 pmol/L), there was an improvement in adynamic bone disease. In those patients with PTH >33 pmol/L, lowering the dialysate Ca also allowed an increase in the dose of vitamin D without consequent hypercalcemia, and a subsequent reduction in PTH. Therefore, reducing dialysate Ca allows more flexible adjustment of vitamin D to correct metabolic abnormalities of bone related to secondary HPT.

Dialysis Ca profiling

One possibility of utilizing the benefits of low dialysate Ca to prevent hypercalcemia but at the same time avoiding intra-dialytic hypotensive episodes is with the use of Ca profiling. In a randomized crossover trial, Kyriazis et al., studied 18 HD patients undertaking 4-hr dialysis with either 1.25 mmol/L Ca dialysate or with 1.25 mmol/L for the first 2 hr and 1.75 mmol/L for the remaining 2 hr, followed by a 4-hr session with 1.5 mmol/L bath.⁵⁹ Hemodynamic effects were comparable between dialysis with either 1.25 mmol/L or 1.5 mmol/L, with hypotension toward the end of treatment sessions. With HD using the combination

of alternate 1.25 and 1.75 mmol/L dialysate Ca (2 hr each), there was a significant reduction in intra-dialytic events, described to be related to an increase in cardiac output with an ionized Ca-induced increase in myocardial contractility. The authors concluded that with the use of profiling, by individualizing the dialysate Ca concentrations used and alternating between them, there may be an improvement in hemodynamic stability, while simultaneously reducing potential problems with hypercalcemia.

Despite only a small sample size, this study demonstrated a possible strategy to help ameliorate intradialytic hypotension, a significant cause of patient morbidity, but longer-term cardiovascular morbidity and mortality as well as effects on renal bone disease have not been analyzed with Ca profiling.

Differing dialysis modalities

Nocturnal hemodialysis (NHD) provides longer and potentially more frequent dialysis and has definitely been proven to provide superior phosphate control compared with conventional hemodialysis (CHD),^{9,60} with NHD patients even being able to discontinue phosphate binders. The elimination of Ca-containing phosphate binders at the commencement of NHD has previously been shown, however, to lead to a loss of up to 8 g of elemental Ca per week in oral intake, and so exacerbate Ca deficiency and secondary HPT.⁶¹ Increasing the dialysate Ca concentration corrects this problem, with an overall net gain of Ca to the patient when using a 1.75 mmol/L Ca bath.

The effects of daily dialysis on Ca balance may differ depending on whether the modality is NHD or short daily (SDHD).^{61–65} The London Daily/NHD Study examined the effect of dialysate Ca concentration on Ca and phosphate metabolism, comparing daily HD (including NHD and SDHD) with CHD.⁶¹ Patients on NHD were initially dialyzing against a 1.25 mmol/L Ca bath with demonstra-

tion of increases in ALP and PTH; predialysis serum Ca levels became lower in patients on NHD within a month. This observational study showed that increasing the dialysate Ca concentration in NHD prevented HPT and bone disease. Those patients on CHD and SDHD still required phosphate binders and did not become Ca deficient on 1.25 mmol/L Ca dialysate. Concerns still exist, though, that higher Ca baths in NHD, however, may potentially contribute to hypercalcemia, vascular calcification, and subsequently more cardiovascular mortality.

Despite the higher Ca levels with increased dialysate Ca, the Ca \times P is reduced on NHD because of much better phosphate control and although long-term mortality data are not yet available, this mode of dialysis certainly provides greater improvements in well-being, cardiovascular outcomes, and bone metabolism.^{61,62,66,67}

IMPACTS OF NEWER PHARMACOLOGICAL MANAGEMENT

Sevelamer and Lanthanum

Sevelamer hydrochloride is a newer phosphate binder containing neither Ca nor aluminum. It is useful for patients requiring better phosphate control and who are also being administered vitamin D metabolites to reduce the potential for hypercalcemia. Sevelamer has been demonstrated to stabilize cardiac calcification and reduce the rate of progression by avoiding or reducing the need for Ca-based phosphate binders, therefore providing a reduction in Ca load.⁶⁸ The Dialysis Clinical Outcomes Revisited (DCOR) study recently demonstrated that patients who used sevelamer experienced a 9% reduction in risk of death from all causes relative to patients using Ca-based phosphate binders over a 2-year period, with mortality influenced by age and duration of treatment.⁶⁹ However, this study did not reveal a significant survival benefit for the non-Ca-based binder, failing to meet its primary or secondary endpoints and showing no significant difference in mortality or morbidity with sevelamer compared with Ca-based phosphate binders.

Interestingly, following the initial published literature revealing the advantages of sevelamer, it was emphasized by Backenroth, in a letter to the editor, that dialysate Ca was not even included in the study.⁷⁰ More recently, the effects of different dialysate Ca concentrations were assessed with the use of sevelamer hydrochloride.⁷¹ With 1.37 mmol/L Ca dialysate, serum Ca levels decreased and PTH levels increased significantly and with 1.25 mmol/L Ca dialysate, there was even transient hypocalcemia. The group with a dialysate Ca of 1.5 mmol/L had unchanged

serum Ca levels and therefore this was the recommended dialysate to reduce acceleration of bone turnover and subsequent development of renal osteodystrophy. Another Japanese study of HD patients also confirmed the necessity of a higher dialysate Ca to prevent worsening secondary HPT when sevelamer is used as a phosphate binder, even with additional active vitamin D supplements.⁷²

Lanthanum carbonate is another newer phosphate binder, although initial concerns with its use surrounded the potential absorption of this element and long-term accumulation in tissues.⁷³ In vitro, it has anticalcification and antiatherosclerotic properties and may be another alternative to Ca-based binders but long-term studies are pending.

Vitamin D analogs

The prescription of active vitamin D is a major treatment to correct hypocalcemia and suppress PTH levels in ESKD. According to the DOPPS data, 52% of patients were treated with some form of vitamin D therapy.¹⁹ Calcitriol (1,25[OH]₂D₃) and alfacalcidol (1 α [OH]₂D₂) have been predominantly used, administered by an oral or an intravenous route, but concerns regarding the risks of hypercalcemia and hyperphosphatemia have led to the emergence of vitamin D analogues that suppress PTH without affecting serum Ca and phosphate levels. Maxicalcitol (22-oxacalcitriol) and doxercalciferol (1 α [OH]₂D₂) have been studied although none have been completely successful in avoiding alterations of Ca and phosphate and to date have not been proved superior to calcitriol and alfacalcidol.⁷⁴

Paricalcitol (19-nor-1,25[OH]₂D₂) is being more commonly used in the United States, perhaps following the retrospective report of reduced mortality in North American HD patients taking paricalcitol rather than calcitriol.⁷⁵ No trials as yet have adequately addressed the implication of these newer vitamin D agents in relation to dialysate Ca levels.

Calcimimetics

The introduction of calcimimetic agents into clinical practice has also had beneficial effects on serum Ca, phosphate, and Ca \times P and have brought increased focus on the increased mortality risk associated with hypercalcemia.⁷⁶ Cinacalcet binds to and activates the Ca-sensing receptor in the parathyroid glands, lowering the threshold for its activation by extra-cellular Ca and diminishing PTH release. Again, similar to the initial trials with sevelamer, dialysate Ca was not considered with the

early study involving cinacalcet and therefore the optimal dialysate Ca bath to be prescribed in the setting of calcimimetics has not been determined.⁷⁷ The use of 1.75 mmol/L dialysate Ca was assessed in a small sample of 7 HD patients, with administration of cinacalcet in patients with severe secondary HPT showing reduction in serum PTH levels and without hypercalcemia.⁷⁷

Recommendations

Recent changes in the management of mineral metabolism in patients with ESKD have placed more emphasis on the concentration of Ca in dialysate. A dialysate Ca concentration of 1.25 to 1.5 mmol/L is often the most appropriate for HD patients. The negative dialysis Ca balance is countered by the oral administration of Ca-based phosphate binders and, if necessary, the use of vitamin D analogues for management of secondary PTH. This allows an overall neutral total body Ca balance.⁷⁸ A newer strategy of re-emerging aluminum-based phosphate binders in some countries and more importantly aluminum-free and Ca-free binders, such as sevelamer and lanthanum, worldwide, can be used for more optimal control of hyperphosphatemia without the excessive Ca load and the risk of exacerbating vascular calcification. With this strategy, it may be necessary to adjust upwards the dialysate Ca concentration with the re-introduction of 1.75 mmol/L dialysate Ca to avoid problems with secondary HPT. The use of noncalcemic vitamin D analogues and calcimimetics also allows for higher dialysate Ca baths.

The decision to use a certain dialysate Ca should be made with results of Ca loading or depleting during dialysis in association with information regarding the oral Ca intake allowing an even total-body Ca balance. The type and degree of renal bone disease and the associated cardiovascular co-morbidities should also influence the individualized dialysate Ca level. Biochemical markers of renal bone disease should be a consideration as a lower dialysate Ca concentration may be an advantage to those HD patients with adynamic bone disease to increase bone formation and resorption. Cardiovascular status should be appreciated when choosing dialysate Ca baths, both with the attempt at reduction of accelerated arteriosclerosis as well as providing hemodynamic stability if there is a degree of LV dysfunction.

Recommendations are that patients taking Ca-based phosphate binders should be dialyzed against Ca of 1.25 to 1.5 mmol/L. Lower dialysate concentrations (1.25 mmol/L) should be used if adynamic bone disease exists with low PTH levels. Dialysate concentrations of 1.75 mmol/L may be used to improve hemodynamics, especially for patients

with LV dysfunction or frequent intra-dialytic hypotension, but with reductions to 1.5 mmol/L should hypercalcemia arise. Higher dialysate Ca concentrations of 1.75 mmol/L may also be necessary for patients whose medication list is free of Ca-based binders and vitamin D supplements, as well as for patients with marked secondary HPT and also those undertaking NHD, although the long-term risk of vascular calcification needs exploration.

Adjustment to the dialysate Ca concentration can change the overall Ca balance to maintain appropriate serum levels of Ca and phosphate and therefore reduce the risks of renal osteodystrophy and cardiovascular disease. Dialysate Ca concentration should be measured and taken into consideration in all studies analyzing serum Ca, calcification, and mineral metabolism in HD patients, and as mentioned more research is warranted to determine the optimal dialysate level.

Response to clinical scenario

With regard to the initial clinical scenario, the predominant aim for this patient would be for better phosphate control and greater suppression of PTH. At the same time, careful monitoring of serum calcium and $\text{Ca} \times \text{P}$ is equally important to reduce the overall cardiovascular risk. If sevelamer is not available, a reduction in phosphate could be achieved through (i) the use of longer, more frequent dialysis such as NHD, (ii) stricter dietary phosphate restrictions, or (iii) the addition of more phosphate binders, possibly extra aluminum hydroxide.

Lanthanum would also be effective as a noncalcium-based phosphate binder, although regulatory restrictions and cost issues in some countries may limit its use if sevelamer is unattainable as well. If there are concerns about aluminum toxicity with aluminum-based binders, an increase in Ca-containing phosphate binders (increasing the currently prescribed calcium carbonate to 3 tablets, 3 times daily) could be an option; however, there is a further risk of exacerbating hypercalcemia. The dialysate calcium concentration in this situation should be lowered and a dialysate calcium level of 1.25 to 1.5 mmol/L is probably most appropriate. With the use of a 1.25 mmol/L Ca bath, there may be an overall negative Ca balance potentially worsening hyperparathyroidism (HPT).

Reducing serum phosphate should also help manage secondary HPT. Noncalcemic vitamin D analogues would probably not provide any additional advantage to the currently prescribed calcitriol, although paricalcitol may prove in further studies to reduce hypercalcemia, vascular calcification, and subsequent mortality and therefore may be more beneficial. The addition of a calcimimetic agent, like

cinacalcet, would be another possible management option to lower PTH without the risk of increasing serum calcium. The optimal dialysate calcium concentrations with the use of cinacalcet and paricalcitol have not been determined although higher levels would most likely be necessary.

If the dialysis modality was changed to NHD with an improvement in hyperphosphatemia and withdrawal of phosphate binders, then 1.75 mmol/L dialysate calcium may be beneficial. This strategy would avoid total body Ca depletion, and subsequent worsening HPT, but still likely reduce Ca \times P because of the impressive reductions in serum phosphate.

Manuscript received February 2006; revised April 2006.

REFERENCES

- Palmer B. Individualizing the dialysate in the hemodialysis patient. *Semin Dial.* 2001; **14**:41–49.
- National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis.* 2003; **42**(Suppl 3):S1–S202.
- Johnson WJ, Goldsmith RS, Beabout JW, Jowsey J, Kelly PJ, Arnaud CD. Prevention and reversal of progressive secondary hyperparathyroidism in patients maintained by hemodialysis. *Am J Med.* 1974; **56**:827–832.
- Slatopolsky E, Weerts C, Lopez-Hilker S, et al. Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med.* 1986; **315**:157.
- Slatopolsky E, Weerts C, Norwood K, et al. Long term effects of calcium carbonate and 2.5 mEq/L calcium dialysate on mineral metabolism. *Kidney Int.* 1989; **36**:897.
- Sawyer N, Noonan K, Altmann P, Marsh F, Cunningham J. High-dose calcium carbonate with stepwise reduction in dialysate calcium concentration: Effective phosphate control and aluminium avoidance in hemodialysis patients. *Nephrol Dial Transplant.* 1989; **4**:105–109.
- Van der Merwe W, Rodger R, Grant A, et al. Low calcium dialysate and high-dose oral calcitriol in the treatment of secondary hyperparathyroidism in hemodialysis patients. *Nephrol Dial Transplant.* 1990; **5**:874–877.
- Llach F, Yudd M. Pathogenic, clinical and therapeutic aspects of secondary hyperparathyroidism in chronic renal failure. *Am J Kidney Dis.* 1998; **32**:S3–S12.
- Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A. Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. *Kidney Int.* 1998; **53**:1399–1404.
- Nolan C, Qunibi W. Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis. *Kidney Int.* 2005; **67**(Suppl 95):S13–S20.
- Malberti F, Surian M, Poggio F, Minoia C, Salvadeo A. Efficacy and safety of long-term treatment with calcium carbonate as a phosphate binder. *Am J Kidney Dis.* 1988; **6**:487–491.
- Argiles A, Kerr P, Canaud B, Flavier J, Mion C. Calcium kinetics and the long term effects of lowering dialysate calcium concentration. *Kidney Int.* 1993; **43**:630–640.
- Fernandez E, Borrás M, Pais B, Montoliu J. Low-calcium dialysate stimulates parathormone secretion and its long-term use worsens secondary hyperparathyroidism. *J Am Soc Nephrol.* 1995; **6**:132–135.
- Argiles A, Mion C. Low-calcium dialysate worsens secondary hyperparathyroidism. *J Am Soc Nephrol.* 1996; **7**:635–636.
- Sherman RA. On lowering dialysate calcium. *Semin Dial.* 1988; **1**:78–79.
- Chertow G, Burke S, Paolo R. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int.* 2002; **62**:245–252.
- Taji Y, Morimoto T, Fukuhara S, Fukui T, Kuwahara T. Effects of low dialysate calcium concentration on health-related quality of life in hemodialysis patients. *Clin Exp Nephrol.* 2005; **9**:153–157.
- Malberti F, Ravani P. The choice of the dialysate calcium concentration in the management of patients on hemodialysis and haemofiltration. *Nephrol Dial Transplant.* 2003; **18**(Suppl 7):37–40.
- Young E, Albert J, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: The dialysis outcomes and practice patterns study. *Kidney Int.* 2005; **67**:1179–1187.
- Locatelli F, Cannata-Andia J, Drueke T. Management of disturbances of calcium and phosphate metabolism in chronic renal insufficiency, with emphasis on the control of hyperphosphataemia. *Nephrol Dial Transplant.* 2002; **17**:723–731.
- Young E, Albert J, Akizawa T, et al. Sevelamer vs calcium-containing phosphate binders and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol.* 2005; **16**:47A.
- Binswanger U. Calcium flux during hemodialysis. *Semin Dial.* 1990; **1**:1–2.
- Argiles A, Mourad G. How do we have to use the calcium in the dialysate to optimize the management of secondary hyperparathyroidism. *Nephrol Dial Transplant.* 1998; **13**(Suppl 3):62–64.
- Malberti F, Surian M, Minetti L. Dialysate calcium concentration decrease exacerbates secondary hyperparathyroidism in dialysis patients given calcium carbonate as a phosphate binder. *J Nephrol.* 1991; **2**:75–81.
- Fabrizi F, Bacchini G, Di Filippo S, Pontoriero G, Locatelli F. Intradialytic calcium balances with different calcium dialysate levels. *Nephron.* 1996; **72**:530–535.
- Ermakova I, Novikov A, Pronchenko I. Use of the equipment for hemodialysis in the diagnosis of calcium me-

- tabolism disorders in terminal chronic renal failure. *Med Tekh.* 1991; **1**:27–29.
- 27 Ulozas E, Chebrolo S, Shanaah A, Daoud T, Leehey D, Ing T. Symptomatic hypocalcemia due to the inadvertent use of a calcium-free hemodialysate. *Artif Organs.* 2004; **28**:229–231.
 - 28 Maynard J, Cruz C, Kleerekoper M, Levin N. Blood pressure response to changes in serum ionized calcium during hemodialysis. *Ann Intern Med.* 1986; **104**:358–361.
 - 29 van Kuijk W, Mulder A, Peels C, Harff G, Leunissen K. Influence of changes in ionized calcium on cardiovascular reactivity during hemodialysis. *Clin Nephrol.* 1997; **47**:190–196.
 - 30 van der Sande F, Cheriex E, van Kuijk W, Leunissen K. Effect of dialysate calcium concentrations on intra-dialytic blood pressure course in cardiac-compromised patients. *Am J Kidney Dis.* 1998; **32**:125–131.
 - 31 Locatelli F, Covic A, Chazot C, Leunissen K, Luño J, Yaqoob M. Optimal composition of the dialysate, with emphasis on its influence on blood pressure. *Nephrol Dial Transplant.* 2004; **19**:785–796.
 - 32 The National Institute of Diabetes and Digestive and Kidney Diseases. *US Renal Data System USRDS 1999 Annual Report.* Bethesda, MD: The National Institute of Diabetes and Digestive and Kidney Diseases; 1999.
 - 33 Foley R, Parfrey P, Samak M. Clinical epidemiology of cardiovascular disease in chronic renal failure. *Am J Kidney Dis.* 1998; **32**(Suppl 3):S112–S119.
 - 34 Block G, Hulbert-Shearon T, Levin N, Port F. Association of serum phosphorus and calcium \times phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am J Kidney Dis.* 1998; **31**:607–617.
 - 35 Giachelli C. Vascular calcification mechanisms. *J Am Soc Nephrol.* 2004; **15**:2959–2964.
 - 36 Moe S, Chen N. Pathophysiology of vascular calcification in chronic kidney disease. *Circ Res.* 2004; **95**:560–567.
 - 37 Goldsmith D, Ritz E, Covic A. Vascular calcification: A stiff challenge for the nephrologist. *Kidney Int.* 2006; **66**:1315–1333.
 - 38 Klemmer P. Calcium loading, calcium accumulation, and associated cardiovascular risks in dialysis patients. *Blood Purif.* 2005; **23**(Suppl 1):12–19.
 - 39 Tetta C, Gallieni M, Panichi V, Brancaccio D. Vascular calcifications as a footprint of increased calcium load and chronic inflammation in uremic patients: A need for a neutral calcium balance during hemodialysis? *Int J Artif Organs.* 2002; **25**:18–26.
 - 40 Haydar A, Covic A, Colhoun H, Rubens M, Goldsmith D. Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. *Kidney Int.* 2004; **65**:1790–1794.
 - 41 Kondos G, Hoff J, Serukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: A 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. *Circulation.* 2003; **107**:2571–2576.
 - 42 Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft F. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis.* 1996; **27**:394–401.
 - 43 Goodman W, Goldin J, Kuizon B, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med.* 2000; **342**:1478–1483.
 - 44 Matsuoka M, Iseki K, Tamashiro M, et al. Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. *Clin Exp Nephrol.* 2004; **8**:54–58.
 - 45 London G, Guerin A, Marchais S, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant.* 2003; **18**:1731–1740.
 - 46 Blacher J, Guerin A, Pannier B, Marchais S, London G. Arterial calcification, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension.* 2001; **38**:938–942.
 - 47 Yoo S, Oh D, Yu S. The effects of low calcium dialysate on arterial compliance and vasoactive substances in patients with hemodialysis. *Korean J Intern Med.* 2004; **19**:27–32.
 - 48 Morrison G, Michelson EL, Brown S, Morganroth J. Mechanism and prevention of cardiac arrhythmias in chronic hemodialysis patients. *Kidney Int.* 1998; **17**:811–819.
 - 49 Nappi SE, Virtanen VK, Saha HH, Mustonen JT, Pasternack AI. QTc dispersion increases during hemodialysis with low-calcium dialysate. *Kidney Int.* 2000; **57**:2117–2122.
 - 50 Sherman R, Bialy G, Gazinski B, Bernholz A, Eisinger R. The effect of dialysate calcium levels on blood pressure during hemodialysis. *Am J Kidney Dis.* 1986; **8**:244–247.
 - 51 Henrich W, Hunt J, Nixon J. Increased ionized calcium and left ventricular contractility during hemodialysis. *N Engl J Med.* 1984; **310**:19–23.
 - 52 Lang R, Fellner S, Neumann A, Bushinsky D, Borow K. Left ventricular contractility varies directly with blood ionized calcium. *Ann Intern Med.* 1988; **108**:524–529.
 - 53 Kyriazis J, Kalogeropoulou K, Bilirakis L, et al. Dialysate magnesium level and blood pressure. *Kidney Int.* 2004; **66**:1221–1231.
 - 54 Fellner S, Lang R, Neumann A, Spencer K, Bushinsky D, Borow K. Physiological mechanisms for calcium-induced changes in systemic arterial pressure in stable dialysis patients. *Hypertension.* 1989; **13**:213–218.
 - 55 Ie E, Vletter W, ten Cate F, Weimar W, Zietse R. Increase in serum ionized calcium during diffusive dialysis does not affect left ventricular diastolic function. *Blood Purif.* 2004; **22**:469–472.
 - 56 Malluche H, Mawad H, Monier-Faugere M. The importance of bone health in end-stage renal disease: Out of

- the frying pan, into the fire? *Nephrol Dial Transplant*. 2004; **19**(Suppl 1):1–13.
- 57 Fiedler R, Deuber H, Langer T, Osten B, Mohan S, Jehle P. Effects of reduced dialysate calcium on calcium-phosphorus product and bone metabolism in hemodialysis patients. *Nephron Clin Pract*. 2004; **96**:c3–c9.
- 58 Hamano T, Oseto S, Fujii N, et al. Impact of lowering dialysate calcium concentration on serum bone turnover markers in hemodialysis patients. *Bone*. 2005; **36**:909–916.
- 59 Kyriazis J, Glotsos J, Bilirakis L, et al. Dialysate calcium profiling during hemodialysis: Use and clinical implications. *Kidney Int*. 2002; **61**:276–287.
- 60 Pierratos A. Nocturnal home hemodialysis: An update on a 5-year experience. *Nephrol Dial Transplant*. 1999; **14**:2835–2840.
- 61 Al-Hejaili F, Kortas C, Leitch R, et al. Nocturnal but not short hours quotidian hemodialysis requires an elevated dialysate calcium concentration. *J Am Soc Nephrol*. 2003; **14**:2322–2328.
- 62 Lindsay R, Alhejaili F, Nesrallah G, et al. Calcium and phosphate balance with quotidian hemodialysis. *Am J Kid Dis*. 2003; **42**:S24–S29.
- 63 Chan C, Murali K, Ilumin M, Richardson R. Improvements in phosphate control with short daily in-center hemodialysis (SDHD). *J Am Soc Nephrol*. 2002; **12**:262A.
- 64 Lugon JR, Andre MB, Duarte ME, Rembold SM, Cruz E. Effects of in-center daily hemodialysis upon mineral metabolism and bone disease in end-stage renal disease patients. *Sao Paulo Med J*. 2001; **119**:105–109.
- 65 Toussaint N, Boddington J, Simmonds R, Waldron C, Somerville C, Agar J. Calcium phosphate metabolism and bone mineral density with nocturnal hemodialysis. *Hemodial Int*. 2006; **10**:280–286.
- 66 Walsh M, Culleton B, Tonelli M, Manns B. A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life. *Kidney Int*. 2005; **67**:1500–1508.
- 67 Veys N, Van Biesen W, Vanholder R, Lamiere N. The effects of long nocturnal dialysis on calcium, phosphate and bone status. *Hemodial Int*. 2003; **7**:83.
- 68 Sadek T, Mazouz H, Bahloul H, et al. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: An open-label, randomized study. *Nephrol Dial Transplant*. 2003; **18**:582–589.
- 69 Suki W, Zabaneh R, Cangiano J, et al. The DCOR Trial—A prospective, randomized trial assessing the impact on outcomes of sevelamer in dialysis patients. *J Am Soc Nephrol*. 2005; **16** (abstract presented, ASN poster 745).
- 70 Backenroth R. Dialysate calcium use in hemodialysis patients. *Kidney Int*. 2003; **64**:1533.
- 71 Izumi M, Shirai K, Ito K, et al. Is 2.5 mEq/L the optimal calcium concentration of dialysate in the use of sevelamer hydrochloride? A study of the dialysate calcium concentration recommended by K/DOQI guidelines. *Ther Apher Dial*. 2005; **9**:24–31.
- 72 Ando R, Naito S, Inagaki Y, et al. The influence of dialysate calcium on the therapeutic effects of sevelamer hydrochloride in hemodialysis patients with secondary hyperparathyroidism under treatment of intravenous vitamin D metabolites. *Ther Apher Dial*. 2005; **9**:16–23.
- 73 Locatelli F, D'Amico M. Lanthanum carbonate. *Curr Opin Cardiol Pulm Renal Invest Drugs*. 2000; **2**:372–377.
- 74 Schroeder N, Cunningham J. What's new in vitamin D for the nephrologists? *Nephrol Dial Transplant*. 2000; **15**:460–466.
- 75 Teng M, Wolf M, Lowrie E. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med*. 2003; **349**:446–456.
- 76 Szczech L. The impact of calcimimetic agents on the use of different classes of phosphate binders: Results of recent clinical trials. *Kidney Int*. 2004;(Suppl 90):S46–S48.
- 77 Touam M, Menoyo V, Attaf D, Thebaud H, Drüeke T. High dialysate calcium may improve the efficacy of calcimimetic treatment in hemodialysis patients with severe secondary hyperparathyroidism. *Kidney Int*. 2005; **67**:2065.
- 78 Cunningham J. Calcium concentration in the dialysate and calcium supplements. *Nephrol Dial Transplant*. 2000; **15**(Suppl 5):34–35.