Dialysate Calcium: A Lot More Than 'Set It and Forget It'

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Nearly all elemental calcium in the human body is found in bone (99%) in the form of apatite and is critical for optimal bone mineralization. The remaining calcium is in plasma, either bound to protein (primarily albumin and globulin), chelated, or circulating as ionized calcium. This ionized calcium has important roles in myocyte and cardiac contractility, nerve conduction, and vascular tone regulation.

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Simplistically, net calcium balance in a patient receiving maintenance hemodialysis is dependent on total dietary intake and the proportion absorbed through the gut; losses in sweat, stool, and urine (the latter of which is minimal in most dialysis patients); and the flux of calcium during dialysis sessions. Dialytic calcium balance is driven by the plasma-dialysate calcium gradient and through convective removal with ultrafiltration. However, this concept of "calcium balance" does not take into account the dysregulated intercompartmental (bone, extracellular fluid, and vasculature) calcium kinetics of dialysis patients resulting in maldistribution.[1]

Calcium homeostasis is normally tightly regulated by 1,25-dihydroxyvitamin D (calcitriol), parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), and calcitonin. However, given abnormalities in all these hormones, impaired phosphate excretion, exogenous vitamin D receptor agonist administration, and the use of calcium-based phosphate binders, understanding the interior milieu of calcium in dialysis patients is challenging. The icing on this complicated cake is dialysate calcium, which can result in significant calcium flux and have important immediate and long-term consequences.

As the search for the optimal dialysate calcium concentration continues, dialysate calcium concentrations commonly used in the United States have changed over time (Fig 1). Initially, a dialysate calcium concentration of 2.5 mEq/L was used because this closely matched the physiologic ionized calcium concentration. However, losses due to ultrafiltration and poor absorption of calcium from the gut due to deficiency of active vitamin D led to widespread hypocalcemia and secondary hyperparathyroidism with resulting hemodynamic and cardiac instability. To avoid these complications, higher calcium loads began being delivered, often with dialysis using a 3.5-mEq/L dialysate calcium concentration (Fig 1).[2] With the recognition that cardiovascular disease was the leading cause of death among dialysis patients and concerns that vascular calcification was complicit in cardiovascular disease risk, the community became more wary of calcium loads that may predispose to vascular calcification. Accordingly, in 2003, the Kidney Disease Outcomes Quality Initiative guidelines suggested that the optimal dialysate calcium concentration was 2.5 mEq/L.[3]

In the last 2 decades, the use of non–calcium-based phosphate binders and cinacalcet in conjunction with emerging data suggesting increased risk for cardiac events with low dialysate calcium concentration have moved the goal dialysate calcium concentration slightly once again, with current KDIGO (Kidney Disease: Improving Global Outcomes) guidelines suggesting a dialysate calcium concentration between 2.5 and 3.0 mEq/L in 2009,[4] albeit based on weak evidence. However, other countries such as Japan routinely use a 3.0-mEq/L dialysate calcium concentration to suppress PTH,[5] while other international organizations have not made definitive recommendations. Clearly, a "one-size-fits-all" approach to dialysate calcium concentration is not appropriate given the need to consider individual patient characteristics, such as cardiac vulnerability, hemodynamic stability, mineral bone disease management, insurance coverage for medications, and perhaps last, the costs associated with variability in dialysate calcium concentrations across facilities. Fueling the controversy[6-8] of what the ideal dialysate calcium concentration should be is the emergence of observational data showing adverse clinical outcomes at both extremes of the dialysate calcium spectrum,[9-11] the lack of clinical trials, and few kinetic and modeling studies, especially those that have used dialysate calcium concentrations other than 2.5 or 3.0 mEq/L.

In this issue of *Kidney Medicine*, Sakoh et al[12] report a prospective study in which the dialysate calcium concentration was increased or decreased to a goal of 2.75 mEq/L. The effect of this change on calcium and phosphate balance, bone turnover markers, and FGF-23 over 24 weeks was evaluated among 24 hemodialysis patients. The study was a prospective intervention performed at 2 hospitals in Japan that until the end of 2012 used only 2.5- or 3.0-mEq/L dialysate calcium concentrations for all patients in their facility. At the time when both facilities were transitioning to a 2.75-mEq/L dialysate calcium concentration, the authors selected 24 men matched for age and cause of kidney disease to participate in the study (12 from each dialysis facility).

Predialysis blood tests and a clinical survey were performed in the middle of the week at the start and at 1, 4, and 24 weeks thereafter. Additionally, intradialytic blood sampling was performed through the dialyzer circuit at the start of a hemodialysis session and after 1 hour, 3 hours,

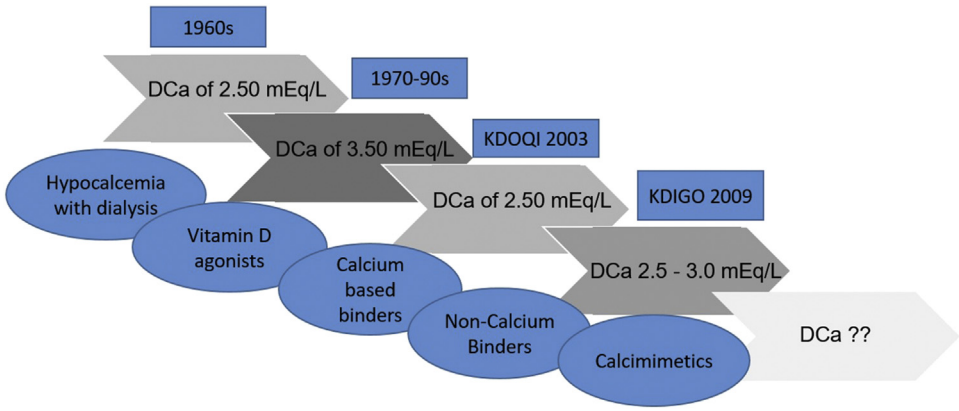

Figure 1. Chronology of dialysate calcium (DCa) concentrations in the United States since the 1960s. The figure shows changes in DCa concentration in the United States since the introduction of long-term hemodialysis along with introduction and changes in medications affecting calcium balance. Abbreviations: KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI. Kidney Disease Outcomes Quality Initiative.

and at the end of dialysis. Dialysate samples (pre- and postdialyzer) were collected at similar time points and the flux of total calcium, ionized calcium, and phosphorus during the hemodialysis session was calculated.

There were no differences in baseline biochemical parameters (serum albumin, calcium, phosphorus, PTH, or FGF-23 levels) between the 2 groups. Mean doses of phosphate binders, vitamin D analogues, and cinacalcet were also similar at the start of the study. Before dialysate calcium concentration conversion, those in the 2.5-mEq/L dialysate calcium concentration group did not have intradialytic elevations in total or ionized calcium levels, whereas those in the 3.0-mEq/L dialysate calcium concentration showed this response by the end of the dialysis session. As expected, at 24 weeks, the 2.5- to 2.75-mEq/L dialysate calcium concentration group showed an increase in intradialytic total and ionized calcium levels. Interestingly, total and ionized calcium levels continued to increase through the dialysis session in the 3.0- to 2.75-mEq/L dialysate calcium concentration group. Despite these differences, during the 24-week study period, predialysis calcium levels did not change significantly in either group. There were also no significant differences between PTH, bone alkaline phosphatase, and TRACP-5b (tartrate-resistant acid phosphatase 5b) levels between the start and 24 weeks in either group.

Before dialysate calcium concentration conversion, the 2.5-mEq/L dialysate calcium concentration group had a net efflux of 59 mg per session, whereas the 3.0-mEq/L dialysate calcium concentration group had an influx of 211 mg per session. Conversion to a 2.75-mEq/L dialysate calcium concentration resulted in the net influx reaching 36 mg per session in both groups. Dialysate calcium concentration conversion did not significantly change intradialytic phosphate, FGF-23, or their predialysis values during the 24-week study period. Finally, doses of phosphate binders, vitamin D analogues, and cinacalcet did not change.

In one of the first studies of intradialytic calcium balance, done nearly 30 years ago, Hou et al[13] evaluated the acute effects of varying dialysate calcium concentrations (1.5, 2.5, and 3.5 mEq/L) on plasma concentrations and dialyzer fluxes of calcium in 7 adult hemodialysis patients during 1 hemodialysis session. They noted that while the 2.5-mEq/L dialysate calcium concentration resulted in no calcium flux, the higher and lower dialysate calcium concentrations were associated with a calcium load and loss, respectively.

Armed with the knowledge of an increased risk for vascular and valvular calcification due to high calcium load, it would be very rare to see a dialysate calcium concentration of 3.5 mEq/L in practice, at least in the United States, because this level always leads to a calcium influx and a net positive calcium balance at the end of dialysis. There have been a number of small studies subsequently that have used varying dialysate calcium concentrations and quantified the calcium mass balance transfer at the end of a dialysis session.[14] All studies using a 3.5-mEq/L dialysate calcium concentration found a net positive calcium mass balance ranging from 80 to 876 mg, while on average, most studies using a 3.0-mEq/L dialysate calcium concentration found a positive calcium mass balance between 46 and 280 mg. Those that used a 2.5-mEq/L dialysate calcium concentration found largely negative calcium mass balance ranging from −6 to −468 mg. Only 1 study used a 2.75-mEq/L dialysate calcium concentration and reported a positive calcium mass balance of 182 mg.[15]

These findings are in line with results reported by Sakoh et al, who also found an influx of calcium into patients when the 2.75-mEq/L dialysate calcium concentration was used.[12] One must note the significant variation (up to 10-fold) in calcium mass balance during dialysis sessions even using the same dialysate calcium concentration. Factors influencing this include differences in populations studied, plasma ionized calcium concentrations, and the volume of

ultrafiltration, which often varies to a large extent between patients, thus causing convective calcium losses. For example, given that ionized calcium is distributed throughout the extracellular fluid, in someone whose extracellular fluid is 15 L, an increase in ionized calcium by 0.2 mEq would correspond to 3 mEq of calcium gained. However, if this person also had 2 L of fluid removed with dialysis, this would result in 3 mEq of calcium lost with a resultant zero calcium balance.[16]

In a crossover trial of 22 anuric patients who underwent three 4-hour dialysis sessions using dialysate calcium concentrations of 2.5, 2.75, and 3.0 mEq/L, investigators found that calcium mass balance was positive with all dialysate calcium levels but increased progressively from dialysate calcium concentration of 2.5 to 3.5 mEq/L.[15] Further, in a study of 25 patients receiving 2.7 mEq/L of dialysate calcium, Waniewski et al[17] performed multiple measurements of calcium in plasma and dialysate and found that a third of patients developed a positive calcium balance after accounting for volume of ultrafiltration using mathematical models. These studies serve as important reminders that as plasma calcium, concomitant medications, diet, bone health, and ultrafiltration volumes change, one must re-address the dialysate calcium concentrations as well.

Lowering the dialysate calcium concentration to a value close to physiologic ionized calcium concentrations has been shown to improve markers of bone and mineral health. In a recent meta-analysis of 7 randomized trials, the use of 2.5 mEq/L of dialysate calcium significantly lowered serum calcium levels and increased PTH levels compared with use of 3.0 mEq/L.[18] Observational data from other studies indicate that increasing the dialysate calcium concentration to >2.5 mEq/L causes reductions in phosphorus, PTH, and vitamin D dosing, with changes being most prominent when dialysate calcium concentrations increased to 3.5 mEq/L. The reverse is observed with decreasing the dialysate calcium concentration.[19] However, the study by Sakoh et al showed no change in PTH and phosphorus levels, and this is not entirely surprising because the change in dialysate calcium concentration was only 0.25 mEq/L in both groups and in addition, the sample size was small.

The main driver for using a dialysate calcium concentration > 2.5 mEq/L is the risk for hemodynamic instability,[20,21] intradialytic hypotension,[22,23] arrhythmias,[10] and increased risk for mortality with low dialysate calcium concentrations. However, studies have also found no association[9,24] or, paradoxically, as shown in the Dialysis Outcomes and Practice Patterns Study (DOPPS), a higher risk for death with dialysate calcium concentrations > 2.5 mEq/L.[25] While disparities in these results stem from heterogeneity in study design, duration of follow-up, ascertainment in outcome, and, most importantly, patient population studied, it underscores the question of whether studies should continue to pursue the holy grail of an "ideal" dialysate calcium concentration.

Studies using dialysate calcium concentrations between 2.5 and 3.0 mEq/L (which KDIGO has suggested be used) are lacking, and in this context, the study by Sakho et al provides interesting primary data despite the paucity of changes in biochemical parameters and lack of clinical outcomes. The goal dialysate calcium concentration should be a spectrum, not a single point. Recognizing that calcium loading and unloading requirements change over time in the same patient is an important first step in individualizing dialysate calcium concentrations to the patient's need. It remains to be seen whether measuring ionized calcium and adjusting dialysate calcium concentrations in real time, as well as the development of kinetic models providing information on calcium mass balance, may help individualize prescription. Until then, clinicians should take into account the individual's cardiac history, hemodynamic stability, baseline mineral parameters, and use of medications affecting calcium balance. It is unlikely that there will ever be an optimal dialysate calcium concentration in the same way there will never be an optimal dialysate potassium concentration for all patients. Until then, use of a 2.75-mEq/L dialysate calcium concentration may be a fairly balanced approach when we have more data for clinical outcomes.

ARTICLE INFORMATION

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