Calcium balance in hemodialysis: More uncertainty than certainty

Abstract
There is controversy about the choice of dialysate calcium concentration (DCa), with strong arguments both in favor of and against the use of a low or high DCa, as they can both be potentially harmful. Evidence suggests that calcium mass balance is positive with a DCa 3.5 mEq/L, negative or neutral with the use of DCa 2.5 mEq/L, whereas both positive and negative balances have been observed with the use of DCa 3.0 mEq/L. Overall, the use of DCa >2.5 mEq/L is usually associated with an increase in serum calcium level and a decrease in serum PTH level and use of lower vitamin D analogue dose, with the opposite effects usually observed with the use of lower DCa. Most of the available evidence is from small-sized and crossover studies; hence, evidence should be regarded with caution and applied in a patient-specific manner. As there are a lot of significant unanswered questions regarding calcium balance and the optimal DCa in hemodialysis patients, further high-quality research is needed to clarify many still unclear aspects of calcium homeostasis and balance in these patients. In conclusion, with the existing evidence the choice of DCa needs to be individualized and contextualized in the setting of each patient’s calcium balance needs and homeostatic response, taking also into account oral calcium intake (dietary and medicinal), any other relevant therapy administered, such as vitamin D analogues, the type of renal mineral bone disorder, and associated cardiovascular comorbidity.

1 | INTRODUCTION
Bone and mineral metabolism disturbances are highly prevalent among patients with end-stage kidney disease treated with hemodialysis (HD) and cause significant morbidity and mortality. Although disturbance of calcium homeostasis is the trigger for the derangement of bone and mineral metabolism observed in chronic kidney disease (CKD), little attention is usually paid in current clinical practice to the choice of the optimal dialysate calcium concentration (DCa). There is controversy about the choice of DCa, with strong arguments both in favor of and against the use of a low or a high DCa, to prevent vascular calcifications in the first case and intradialytic hypotension, cardiac arrhythmias, and secondary hyperparathyroidism (SHPT) in the second one. Historically, the recommendations have also changed significantly depending on the DCa that fitted better with the dominant phosphate-binders in use at the time. Thus, the initially favored DCa 2.5 mEq/L changed in favor of 3.0 mEq/L during the aluminum phosphate-binder era because of the emergence of SHPT due to low calcium intake, to change again after the 1990s in favor of a DCa 2.5 mEq/L due to the extensive use of calcium-based phosphate binders and vitamin D analogues and the ensuing risk of hypercalcemia. In the 2000s with the increasing use of calcium-free phosphate binders and calcimimetics, the debate has re-emerged in view of evidence suggesting that both low (<3.0 mEq/L) and high (>3.0 mEq/L) DCa can have potentially beneficial and harmful effects. In 2003 KDOQI guidelines recommended DCa 2.5 mEq/L whereas for the first time they also suggested limiting calcium intake through the phosphate binders and the diet; in 2005 the same guidelines for children recommended using DCa 2.5 mEq/L in patients treated with calcium-based phosphate binders and DCa 3.0 mEq/L for patients not receiving calcium salts, taking into account serum calcium levels and the use of vitamin D analogues. The KDIGO guidelines in 2009 and 2017 suggested a narrow range of DCa (from 2.5 to 3.0 mEq/L), along with restriction of the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analogues in the presence of persistent or recurrent hypercalcemia, arterial calcification and/or if serum PTH levels were persistently low. However, these suggestions are still debatable as it is argued that in the majority of dialysis patients the use of DCa <2.5 mEq/L is necessary to prevent long-term calcium accumulation.

2 | CALCIUM DISTRIBUTION AND HOMEOSTASIS
More than 99% of total body calcium (approximately 1200 g in adults) is located within the bones in the form of calcium-phosphate complexes, mainly hydroxyapatite. The remaining 1% of the total body calcium is distributed in either nonionized (~50%) or ionized (~50%) forms. Nonionized calcium in turn is found either...
as complexed with anions such as phosphate, bicarbonate, and citrate (complexed Ca) or bound to proteins, mainly serum albumin (~90%) and globulin (~10%) in serum and intracellular calmodulin (protein-bound Ca) within the intracellular and extracellular space in various tissues, especially skeletal muscle (Figure 1). Although all calcium in the body is technically ionized, the term usually only applies to the free ionic fraction that is physiologically active in the blood. Together, ionized and nonionized complexed calcium constitute the diffusible/ultrafilterable or free fraction of calcium, since it passes through biologic membranes as opposed to protein-bound calcium, which is not diffusible. Nonionized complexed calcium diffuses rapidly across a steep concentration gradient between the intracellular and extracellular milieu, and in this way body calcium is in constant and rapid exchange within the various calcium pools and is responsible for a wide range of essential extra- and intracellular functions.

The tight control of the distribution of calcium is of high physiological importance and is regulated by calcium homeostasis through an integrated hormonal system that controls calcium transport in the gut, intravascular/extracellular space, kidney, and bone. It involves serum ionized calcium, the calcium-sensing receptor and two major calcium-regulating hormones, PTH and 1,25(OH)2D and their receptors, the PTH receptor and the vitamin D receptor, respectively. Further complicating calcium homeostasis is the fact that it is intertwined with phosphate and magnesium homeostasis. The details of calcium homeostasis have been reviewed elsewhere.9,10 Calcium homeostasis in CKD is extensively disturbed leading to abnormal calcium balance. Thus, positive calcium balance is observed in patients with CKD stage 3b/4 onwards with oral intake of calcium from diet or binders of 800—1000 mg/day and above.10 In advanced stages of CKD deposition of calcium together with phosphate or other anions can also occur in soft tissues, typically in the form of vascular, valvular, and other extraosseous calcifications.

3 | CALCIUM BALANCE IN HD

Calcium balance refers to the net calcium intake minus total calcium output. Normally, homeostasis and balance are coupled such that the process of homeostasis responds appropriately to maintain appropriate balance. In patients with CKD, however, homeostatic mechanisms are seriously disturbed; hence, there is uncoupling of calcium homeostasis and balance. The capacity to excrete calcium in the urine is seriously compromised in advanced stages of CKD and completely lost in anuric patients. The efficiency with which the rapidly exchangeable bone pool is able to absorb/mobilize calcium also appears to be affected by serum phosphate level, acidosis, increased age, and diabetes mellitus. The situation is even more complex in dialysis patients due to the variable intradialytic effects of DCA, the variable intestinal calcium absorption associated with different vitamin D analogues, the expanded internal calcium pool related to soft-tissue calcification, the unpredictable calcium excretion via residual urinary output, and calcium losses through the skin. As calcium intake and output is difficult to estimate, calcium balance is very difficult to calculate in daily clinical practice. In this context, serum calcium levels is a rather poor indicator of the total body stores and balance and, although disturbances of serum calcium levels indicate serious disruption of calcium homeostasis, on their own they do not reflect calcium balance. Similarly, it has been shown that the intradialytic changes in serum calcium level do not correlate with the observed external net calcium transfer,11 apparently as a result of the rapid response of calcium homeostatic mechanisms.

4 | THE CHOICE OF DCA IN CONVENTIONAL HD

HD process affects circulating calcium by both diffusive and convective transport. As mentioned above, it is only the ionized and the nonionized complexed calcium (roughly 60% of the total circulating calcium) that is diffusible/ultrafilterable and hence influenced by HD. Gain or loss of calcium by the patient during a HD session are determined by the inlet dialyzer diffusion concentration gradient between the diffusible/ultrafilterable calcium levels in plasma water and the DCA (importantly, it has been shown that dialysate labels overestimate the actual mean ionized calcium concentration in the dialysate by 10%–20%12), as well as by the ultrafiltrate volume, which determines not only calcium removal but also hemoconcentration. The activity of the exchangeable pool in the skeleton and possibly in soft-tissue calcifications as well as the intestinal absorption are equally important determinants of calcium balance during HD, although admittedly very difficult to assess in clinical practice. Furthermore, when considering calcium clearance during extracorporeal therapies, changes in serum bicarbonate, pH, and magnesium homeostasis have to be considered. Recently proposed novel calcium kinetic models might prove to be helpful toward a more accurate assessment of calcium balance on HD.13,15

Compelling evidence suggests that calcium mass balance is always positive with a DCA 3.5 mEq/L, negative or neutral with the use of DCA 2.5 mEq/L, whereas both positive and negative balances have been observed with the use of DCA 3.0 mEq/L.16-20 Both the 2009 and 2017 KDIGO Guidelines considered that the use of DCA 2.5 mEq/L would yield neutral calcium balance.6,7 More recent evidence suggests that a DCA 2.75 mEq/L might be preferable as it causes just a
mildly positive calcium balance while maintains optimal serum calcium and PTH levels.26 Variable calcium balances with the same DCa that have been reported in different studies obviously are accounted for by the variability in baseline serum ionized calcium concentration and the ultrafiltrate volume, but probably also by differences in population characteristics as well. High ultrafiltrate volumes in fact can lead to remarkable convective calcium loss which occasionally might even exceed any calcium gains through diffusion.27 Other factors that have not been looked upon in most studies, such as bicarbonate, pH, and magnesium balance, the use of citrate or oral calcium intake, might also partially account for the variations of the results observed. Overall, switching to DCa >2.5 mEq/L is usually associated with an increase in serum calcium level and a decrease in PTH level and use of vitamin D analogue dose,24 with the opposite effects usually observed when switching to lower DCa.28,29

Calcium profiling with a time-profiled increase in DCa during the dialysis session has been suggested as a potential answer to the ongoing debate on the optimal DCa. Kyriazis et al20 were the first to show that increasing DCa from 2.5 to 3.5 mEq/L during the last 2 hours of the session may reduce the hypotension events.21 DCa profiling seems to retain the advantages of high calcium in terms of hemodynamic stability and modification of corrected QT interval (QTC) while reducing the excessive positive calcium balance typical of dialysis with high DCa.

5 | THE CHOICE OF DCA IN EXTENDED HD AND HEMODIAFILTRATION

Extended HD, either daily or nocturnal, is associated with more excessive bone mineral loss compared to standard HD and therefore these patients usually require a higher DCa, typically DCa 3.0 mEq/L, to avoid calcium depletion and hypocalcaemia that in turn could lead to SHPT and osteopenia.32-34 This problem is usually compounded in patients who discontinue calcium-based phosphate binders due to increased phosphate removal. On the contrary, most patients on online hemodiafiltration (OHDF) will be in a positive calcium balance, which is also associated with lower serum PTH levels and more potent response to vitamin D.35,36 It is the convective clearance of calcium that has the major impact on calcium balance with only a minor impact from any diffusive clearance. The effect of convective techniques on calcium balance depends mainly on the infusion site of the substitution fluids, with predilution mode resulting in a more positive calcium balance compared to predilution. Predilution mode will also have the least effect on diffusive clearance. The impact of the calcium composition of the substitution fluids and the calcium removed by ultrafiltration is rather minor. As such, calcium mass transfer in OHDF is also affected by the infusion mode. For a given concentration gradient between blood and dialysate, calcium balance in predilution OHDF will be lower than in HD and often negative especially with higher ultrafiltration rates and targeted weight loss, whereas in postdilution OHDF may be similar or higher than in conventional HD, depending upon the amount of ultrafiltration.

Based on this observation, it is suggested to lower the DCa during postdilution HDF37 and increase it by approximately 0.5 mEq/L when switching treatment from HD or postdilution OHDF to predilution OHDF.38

6 | CLINICAL CONTEXT

The choice of DCa needs to be individualized and contextualized in the setting of each patient’s calcium balance needs and homeostatic response, taking also into account oral calcium intake (dietary and medicinal), any other relevant therapy administered, such as vitamin D analogues, the type of renal bone mineral disorder, and associated cardiovascular comorbid conditions. Positive calcium balance can lead to PTH oversuppression, adynamic bone disease, hypercalcemia, and soft-tissue calcification, which are associated with adverse cardiovascular outcomes.39 On the other hand, low DCa is associated with hypocalcaemia which may lead to cardiac rhythm disturbances, typically QTc prolongation, myocardial ischemia, and stunning,42 and hypotension due to decreased vascular resistance and lower cardiac output.

1. **Adynamic bone disease**: In the presence of adynamic bone disease the use of a low DCa, probably 2.5 mEq/L, may be appropriate as it has been shown to increase serum PTH and bone-specific alkaline phosphatase.40,41 Concomitant restriction of noncalcium-based phosphate binders and discontinuing or reducing the dose of active vitamin D sterols may also be warranted.42

2. **SHPT**: For patients with SHPT, the use of a DCa 2.75–3.0 mEq/L may be advisable.24 A lower DCa (eg, 2.5 mEq/L) with an increased dose of vitamin D analogues and calcium-based phosphate binders could be used instead, at the expense, however, of a higher serum phosphate level.32 The introduction of cinacalcet which simultaneously reduces serum PTH, fibroblast growth factor-23, and serum calcium necessitates even more the use of a higher DCa,45 which in turn may allow the suppression of PTH secretion with lower doses of the calcimimetic.28

3. **Postparathyroidectomy**: It is reasonable to opt for a high DCa aiming at a positive calcium balance since in patients with severe SHPT recovering from osteitis fibrosa bone formation is greater than bone resorption.3

4. **Calcific uremic arteriolopathy**: For patients with calcific uremic arteriolopathy, the optimal DCa remains unclear. Several investigators have reported the use of a low DCa in association with other interventions, such as discontinuing warfarin and vitamin D analogue therapy, switching to noncalcium-based phosphate binders, and adding medications such as prednisone and sodium thiosulfate.44,45 It seems appropriate to aim for an overall negative calcium balance with the use of low DCa, probably 2.5 mEq/L, with appropriate monitoring of the QT.

5. **Vascular stiffness**: An increase in arterial stiffness is associated with an increased risk of cardiovascular morbidity and
mortality.\textsuperscript{46,47} Calcium has been implicated as a potential mediator of arterial stiffness and emerging evidence suggests that increasing acutely DCa from 2.0 to 3.0 mEq/L results in an increase in arterial stiffness; this effect, however, was not confirmed in the long-term.\textsuperscript{48,49} The importance of these results remains unclear and the longer term effects of an increase in DCa are not clear.

6. Cardiovascular calcification: The development of cardiovascular calcification is complex but has been associated with disorders of bone and mineral metabolism, calcium intake (specifically orally), and high risk of cardiovascular morbidity.\textsuperscript{50} and mortality.\textsuperscript{51} Importantly, there is no clear evidence that vascular calcification is reversible. Existing evidence suggests that a positive calcium balance in dialysis patients may induce ectopic calcification regardless of the presence of hypercalcemia.\textsuperscript{52} Although the role of DCa on progressive vascular calcification is not clear, it is reasonable to avoid using high DCa, especially in patients with presumed adynamic bone disease. Other methods to restrict overall calcium intake should also be considered.

7. Intradialytic hypotension: Several case control studies suggested that DCa may have an important impact on intradialytic blood pressure,\textsuperscript{52,53} probably due to an impact of serum ionized calcium on systemic vascular resistance and cardiac output.\textsuperscript{54} Compared to low DCa, a higher DCa increases sympathetic activity, leading to better hemodynamic stability during HD.\textsuperscript{55} With DCa profiling, hemodynamic stability improved and there was a reduction in saline solution infusion requirements compared to a 4-hour treatment with a DCa 2.5 or 3.0 mEq/L.\textsuperscript{56} Although hard evidence is still missing, a higher DCa should be considered for patients with cardiac impairment who are prone to intradialytic hypotension.

8. Risk of sudden cardiac death: Several studies have shown that the use of DCa 2.5 mEq/L, especially with a potassium dialysate concentration of 2.0 mEq/L, is associated with an increase in the length of the QT and higher rates of sudden cardiac death presumably through the ensuing risk for torsades de pointes.\textsuperscript{57-58} For HD patients believed to be at a greater risk for sudden cardiac death, use of a low DCa should be avoided especially in patients at risk of hypokalemia at the end of the dialysis session.\textsuperscript{59}

7 | CONCLUSIONS

Most of the available evidence is from small-sized and crossover studies and not from randomized controlled trials; hence, evidence should be regarded with caution and applied in a patient-specific manner. As there are a lot of significant unanswered questions regarding calcium balance and the optimal DCa in dialysis patients, further high-quality research is needed to clarify many still unclear aspects of calcium homeostasis and balance in these patients. Suggestions for future research should include the effect of different DCa on patient outcomes, the role of DCa in progressive calcification and vascular stiffness and any potential effects on patient outcomes, the effects of low DCa on blood pressure and relation to sudden cardiac death, the potential differences between the different sources of calcium intake (DCa vs oral calcium), the potential impact of any DCa choices on bone stoichiometry, as well as the best clinically meaningful index of calcium balance in patients on HD.

In conclusion, with the existing evidence the choice of DCa needs to be individualized and contextualized in the setting of each patient’s calcium balance needs and homeostatic response, taking also into account oral calcium intake (dietary and medicinal), any other relevant therapy administered, such as vitamin D analogues, the type of renal bone mineral disorder, and associated cardiovascular comorbid conditions.

DISCLOSURE

The authors have no interest to disclose.

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REFERENCES

7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD.


