Dialysate Calcium Levels: Do They Matter?

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Abstract

Background: Calcium (Ca) is an essential element that plays a critical role in many biological processes. In dialysis patients, the regulation of Ca balance is highly complex, given the absence of kidney function, endocrine disturbances and the use of drugs such as phosphate binders, vitamin D analogues, and calcimimetics. Also, the use of different dialysate Ca (Dca) baths has profound effect on Ca balance, which depends both on the difference between the Ca concentration in the bath and the serum of the patients, as on the ultrafiltration volume. **Summary:** The choice of Dca may have important short- and long-term consequences. While lower Dca (especially <2.5 mEq/L) concentrations have been associated with an increased risk of sudden cardiac death in observational studies, Dca in the higher ranges (3.0 mEq/L and above) may contribute to vascular pathology. Intra-dialytic hemodynamics may also be affected by the choice of Dca. In general, lower Dca concentrations are associated with an increase, and higher Dca concentrations with a decrease in

parathyroid hormone (PTH) levels. Preliminary data has suggested that a Dca of 2.75 mEq/L may help in obtaining a net zero intradialytic Ca balance in individual patients, but clinical experience is still limited. **Key Message:** The optimal Ca balance depends on multiple parameters including blood Ca levels, PTH and the use of phosphate binders and vitamin D analogues, as well as on the risk of hemodynamic stability and cardiac arrhythmias. Therefore, Dca prescription should be individualised. A Dca of 2.75 mEq/L may be useful adjunct for dialysis providers.

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Introduction

Calcium (Ca) is an essential element that serves an important role in skeletal mineralization. More than 99% of the Ca in the body is stored in bone as hydroxyapatite. Ca in this form provides skeletal strength as well as a reservoir for Ca to be released into the serum [1].

Plasma Ca (pCa) accounts for less than 1% of the total body Ca, and exists in 3 forms: protein-bound, ionized (free; iCa), and complexed (chelated) [2–4]. Protein-bound Ca, which accounts for 40% of the pCa, cannot be

used by tissues. Albumin and globulin are the primary Ca-binding proteins in the serum, whereas calmodulin is the primary Ca-binding protein in the cell. Complexed Ca, which accounts for 9% of the pCa, allows Ca to be absorbed by various tissues or carried in between the many parts of the body. Free Ca, which makes up 51% of the pCa, is utilized by the body to maintain physiologic functions. Ca plays a critical role in many biological processes, including cardiac conduction and contractility, regulation of vascular smooth muscle tone and nervous conduction, and is therefore tightly regulated and in a constant state of flux with the Ca pool in bone.

Homeostasis of Ca

Homeostasis of Ca is maintained by actions of hormones that regulate Ca transport in gut, kidneys and bone [5]. The Ca concentration is regulated by multiple hormonal pathways including parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), fibroblast growth factor 23, calcitonin and oestrogen. The parathyroid glands release PTH in response to a decrease in iCa. PTH acts on the kidneys to increase Ca reabsorption in the ascending loop of Henle, the distal convoluted tubule and the collecting duct. Plasma calcitriol concentrations are regulated by PTH, the Ca and phosphate concentrations and fibroblast growth factor 23. Calcitriol increases the Ca concentration through effects on the gastrointestinal tract, bone and the kidney. PTH acts on the bones to stimulate osteoclasts involved in bone reabsorption and the release of free Ca. All these processes contribute to the rise in Ca. In turn, calcitonin is released by the thyroid parafollicular cells in response to an increase in Ca and acts on the bones to stimulate osteoblasts to deposit Ca in bones. Calcitonin also inhibits renal reabsorption of Ca and inhibits Ca absorption in the intestines. These processes lead to a decrease in Ca.

In haemodialysis (HD) patients, the regulation of Ca balance is highly complex, given abnormalities in PTH and calcitriol levels, and the use of Ca-based phosphate binders (CaBi) and vitamin D analogues. The prescription of the dialysate Ca (DCa) bath also has a major influence on overall Ca balance [6, 7] and can thus be considered an important pharmaceutical in the treatment of ESRD patients. Importantly, the DCa can have both short- and long-term effects.

The most appropriate DCa concentration for individual patients requires balancing potential benefits of a higher DCa (control of PTH, improved hemodynamic stability) against potential risks (vascular calcifications, adynamic bone disease). Unfortunately, there is a paucity

of high-quality clinical evidence, which Ca balance should be targeted to best address these potential benefits and risks [6, 8, 9]. This makes it challenging to define the optimal DCa in the individual patient [10].

History of DCa Prescription

During the introduction of chronic HD in the 1960s, a DCa of 2.50 mEq/L (1.25 mmol/L) close to the physiological concentration of ionized Ca (iCa) in the blood (1.25 mmol/L or 2.50 mEq/L) was used [11]. At that time no effective drug was available for the control of secondary hyperparathyroidism and consequently hypocalcaemia and severe secondary hyperparathyroidism were almost invariably observed. Clinically hypocalcaemia exacerbated intradialytic hemodynamic instability and drove the development of high turnover renal osteodystrophy. To overcome these problems, in the following years, a DCa of 3.50 mEq/L (1.75 mmol/L) has been considered optimal in HD [12]. This essentially provided an intravenous Ca infusion during HD. A DCa of 3.5 mEq/L was used for a long time, even after CaBi almost completely replaced aluminium hydroxide and when calcitriol, in the mid-70s, and other potent vitamin D analogues became available. In the 1980s, there was an increasing awareness that the pursuit of this strategy, in combination with calcitriol and CaBi, was capable of precipitating hypercalcaemia. This led to the recommendation of a DCa of 2.5 mEq/L (1.25 mmol/L) by K-DOQI, whereas the more recently published Kidney Disease: Improving Global Outcomes recommend a DCa between 2.5 and 3.0 mEq/L [13, 14]. Also there is a trend towards further reduction in the default DCa concentration in recent years [10].

Short- and Long-Term Effects of DCa on Clinical Outcomes

The transfer of Ca during dialysis has both short- and long-term potential consequences. During and immediately after dialysis the effects are largely hemodynamic, altering cardiac function as well as peripheral vascular tone and conduit arterial compliance. Changes in iCa levels play a pivotal role in myocardial contractility during dialysis. Studies have demonstrated a lower myocardial contractility in patients treated with a DCa of 2.5 mEq/L as compared to those treated with a DCa of 3.5 mEq/L (1.75 mmol/L) [15, 16]. In one study, the change in mean arterial pressure during HD was inversely related to the change in iCa [17]; in 2 other studies, the decline in blood pressure was less with a DCa of 3.5 mEq/L compared with 2.5 mEq/L [16, 18]. In another study, no difference in the blood pressure response between high and low DCa was

found [19]. Cardiac arrhythmias are more common in patients being treated with a DCa below 2.5 mEq/L and they also increase the risk of sudden cardiac death [20, 21], which may be possibly related to a prolongation of the QT interval with low DCa levels [21, 22]. Interestingly, in a recent study, the authors demonstrated that a DCa of 3.5 mEq/L compared with 2.5 mEq/L was associated with an increase in the heart rate variability LF/HF ratio, denoting higher sympathetic activity when compared to low DCa [23]. These findings suggest that a higher DCa increases sympathetic activity, leading to better hemodynamic stability during HD.

On the longer term, the use of a higher DCa will result in a positive Ca mass balance (CaMB) that might affect (along with multiple other influences) the development of cardiovascular calcification and renal bone disease. A DCa of 3.5 mEq/L is, as mentioned earlier, effective in decreasing PTH levels and bone turnover but might also lead to hypercalcemia and metastatic calcification. In the DOPPS (Dialysis Outcomes and Practice Patterns Study), more than 50% of patients with hypercalcemia were being treated with a DCa higher than 2.5 mEq/L [24], and that a higher DCa was associated with increased mortality. In a single-centre randomised trial in 128 patients, He et al. [25] showed that patients randomized to a DCa of 2.5 mEq/L had a significantly lower pulse wave velocity and intima media thickness as compared to patients randomized to a DCa of 3.0 mEq/L, whereas mortality after 2 years was lower in the DCa 2.5 mEq/L group (5/64 vs. 13/64; $p = 0.041$). On the contrary, in another study, a DCa of 3.5 mEq/L was not associated with an increased mortality [26]. In a more recent single-centre study including 128 patients undergoing maintenance HD, the authors showed that increasing the DCa from 3.0 to 3.5 mEq/L reduced PTH and phosphorus, lowered the doses of Ca and vitamin D3 required and was well tolerated for short periods of time with no increase in mortality rate [27]. Although, in this study, there was a long follow-up period of up to 10 years, patients came from 3 different centres and other factors such as variations in laboratory values over time and dietary factors were not considered.

In a study including more than 350 clinics, the transition from a DCa concentration of 2.5 to <2.5 mEq/L (so-called converter clinics) with clinics that continued to use a DCa concentration of 2.5 mEq/L (control clinics) were compared [28]. The authors found no significant differences between the 2 groups with respect to all-cause mortality or hospitalization rates. As could be expected from previous publications [28–30], there was a relative increase in the rate of hypocalcemia observed among pa-

tients at converter clinics compared with control clinics. This decrease in Ca levels occurred despite an increase in PTH and increased use of CaBs and vitamin D. Importantly, clinics that changed their DCa to <2.5 mEq/L had significantly higher rates of hospitalization for congestive heart failure than control clinics. Moreover, intradialytic hypotension was also significantly more likely to occur in these clinics.

In a subanalysis of the EVOLVE trial, no difference in the primary composite endpoint, cardiovascular death or sudden cardiac death was observed between patients treated with DCa of respectively <2.5, 2.5, or >2.5 mEq/L [31] in an adjusted analysis. Also, no significant relation between the dialysate to Ca gradient and clinical outcomes was observed in this study. In a recent meta-analysis [32] of 7 randomized trials, a low DCa (2.25 or 2.5 mEq/L) was associated with lower pCa and higher PTH levels as compared to higher DCa (3.0 or 3.5 mEq/L) without differences in mortality, whereas the effect on vascular calcification appeared to be inconsistent. To summarise, the evidence at present provides some support for a beneficial effect of DCa 2.5 mEq/L levels on clinical endpoints as compared to higher DCa levels but is still not completely consistent. DCa concentrations lower than 2.5 mEq/L have been associated, albeit in observational trials, with an increased risk of sudden cardiac death. Given the wide variety of factors involved in Ca homeostasis, a relevant question is whether assessment of the CaMB might aid in treatment prescription.

CaMB in Hemodialysis

In HD patients, CaMB is determined by the difference between Ca absorbed between dialyses and the Ca removed during dialysis. CaMB during HD is influenced by both diffusive and convective transport. The driving force that determines the diffusive transport is given mainly by the inlet dialyzer diffusion concentration gradient between the iCa levels in the dialysate and in the plasma water, which depends on a rapidly mobilizable extracellular Ca pool [33]. CaMB is influenced also by the convective transport, the amount depending on the Ca concentration in the spent dialysate and the volume of ultrafiltration [34]. Chronic Ca overload is considered one of the main factors contributing to the high rate of vascular and valvular calcifications in HD patients. The achievement of a net zero, or depending on the use of CaBi and vitamin D analogues, even net negative CaMB over the HD, may thus be a relevant clinical goal. On the other hand, a net negative CaMB may lead to worsening of high turnover bone disease and osteoporosis and might be a risk factor

for intra-dialytic morbid events, as discussed previously. Ideally therefore, the optimal DCa prescription should take these multiple factors into account [8].

Regarding the calculated CaMB during conventional HD (i.e., ± 4 -h sessions), this is always positive with a DCa of 3.5 mEq/L, and, when regarded as a mean of the study population, tends to be negative during DCa of 2.5 mEq/L. However, in different studies, both a positive and negative DCa were observed during a DCa of 3.0 mEq/L [34, 35]. Other studies have showed that the use of a DCa of 2.5 mEq/L had in general a neutral effect on SCa levels, but with variable effects on CaMB [36].

Differences between study populations and individual patients likely depend on variations in the plasma to DCa gradient and the ultrafiltration volume, which are the main determinants of CaMB during dialysis [36]. Recent studies suggest that a DCa in the middle of 2.5 and 3.0 mEq/L might be preferable because it gives a mildly positive CaMB, maintains normal SCa and does not stimulate short-term PTH secretion during dialysis [37]. In a more recent study, Waniewski et al. [38] observed a mean weekly dialytic removal of 12.8 mmol Ca in 17 patients and a net absorption of 9.5 mmol/week in 8 patients with a DCa of 2.7 mEq/L.

In a randomized crossover trial using 3 different DCa concentrations of 2.5, 2.75 and 3.0 mEq/L were among others CaMB measured from the dialysate side [39]. Total CaMB were respectively $+75 \pm 122$, $+182 \pm 125$, and $+293 \pm 228$ mg. The authors found that a DCa of 2.75 mEq/L produced a mild positive CaMB while maintaining normal plasma water iCa levels and did not stimulate PTH secretion.

In the context of the DialysisIS study, a more rigorous method capable of quantifying the intradialytic CaMB was proposed [35]. The proposed single-pool variable-volume kinetic model, tested in patients treated with a DCa concentration of either 3.0 or 3.5 mEq/L took into account all aspects of diffusive and convective exchange using bicarbonate dialysis. The results of the study showed that when patients were dialysed against a DCa of 3.0 mEq/L, the difference between predicted and measured values of iCa was 0.02 mmol/L. With a mean ionized DCa concentration of 2.5 mEq/L, CaMB was on average negative. The predialysis ionized plasma water concentration and total ultrafiltrate were the most important predictors of CaMB. The results of this study may help in the prediction and quantification of intradialytic CaMB and can evaluate the eventual Ca transfer outside the extracellular pool in clinical practice.

The involvement of bone tissue in acute Ca regulation, independent of cell-mediated remodelling, has already been proposed in the 1970s but it did not receive much attention until recently [40, 41]. Ca perfusion experiments in dogs demonstrated Ca exchange fluxes of more than 6,000 mg/day between extracellular fluid and bone surface under physiologic conditions [42]. To avoid a positive CaMB, the guidelines generally suggest a DCa of 2.5 mEq/L for most HD patients based on relatively stable intradialytic serum Ca using this DCa [14]. However, it has been demonstrated that this might underestimate the amount of Ca that is transferred into chronic HD patients during each HD session using a DCa of 2.5 mEq/L [33]. A rapidly exchangeable Ca pool located at the bone level has been previously proposed to be involved in acute (minute-to-minute) extracellular Ca regulation [43]. To evaluate the contribution of this pool in the maintenance of serum Ca levels, acute Ca buffer capacity was assessed by measuring intradialytic dialysate-sided iCaMB and change in extracellular fluid Ca mass in chronic HD patients using a DCa of 3.5 and 2.5 mEq/L [44]. Osteocalcin was measured before HD. Interestingly, the authors found that iCaMB was invariably positive for both 2.5 and 3.5 mEq/L DCa. Using a DCa of 3.5 mEq/L, an independent association of acute Ca buffer capacity with undercarboxylated osteocalcin was demonstrated. The data suggests the existence of a rapidly exchangeable Ca pool that counteracts acute serum Ca deviations in HD patients.

Finally, the use of citrate HD may have an effect on CaMB. In a randomized controlled trial using regional citrate anticoagulation (RCA), patients were assigned to normal or low iCa target [45]. Mean delivered Ca during the dialysis treatment was 58.3 ± 4.8 mmol in the normal and 51.5 ± 8.2 mmol in the low iCa group ($p = 0.010$), which resulted in a significantly higher mean positive CaMB of 14.6 ± 8.3 mmol (584 ± 333 mg) per procedure in normal as compared to 7.2 ± 8.5 mmol (290 ± 341 mg) in the low iCa group ($p = 0.024$). To achieve a more neutral CaMB and allowing a mild hypocalcemia during HD with RCA, especially when it is used for prolonged periods, the use of RCA might be an alternative for controlling CaMB. However, more research is needed before implementing it in daily clinical practice, especially after reviewing the side effects.

Does an Optimal DCa Exist?

Optimal or appropriate DCa is defined as the concentration needed to maintain an optimal bone and vascular health. However, data to underline this statement is

unfortunately lacking. Therefore, it seems appropriate that the DCa should be optimised to maintain a “neutral” balance in the fully grown adult, also taking into account the dietary intake and the use of P-binders. It has been suggested to lower the DCa to remove Ca during the dialysis procedure, so that extra CaBi can be given during the interdialytic period [7]. However, the net effect depends on the complex interplay of Ca with the bone pool, the stimulatory and inhibitory effects of Ca modulation on the parathyroid gland, and the resultant effects on bone and vascular biology [46]. A more physiologic approach would be to maintain neutral Ca balance during dialysis and adjust the interdialytic Ca intake within the current Institute of Medicine’s recommendation for healthy adults of 800–1,200 mg of elemental Ca per day [47]. However, there are several barriers to individualization such as the fact that DCa is mostly given on a facility basis, the cost efficacy of individualization, or time consuming [9]. Optimal and precise individualization would also require the development of HD machines that are capable of measuring iCa and adjusting the DCa concentration in real time. However, information on CaMB and Ca transfer also needs to be taken into account. Ideally, a model that gives information on the CaMB during dialysis would be of great help in preventing side effects of both a positive and/or negative CaMB. Recently, a two-compartmental

patient model, taking into account the Ca-albumin binding and varying protein concentration (Gibbs-Donnan effect) and spatiotemporal representation of dialyzer model, was developed to investigate and quantify the CaMB during dialysis [48]. The simulations made by the model suggest that with a DCa of 1.25 mmol/L, patients may also be loaded with Ca during dialysis. This net Ca flux from dialysate to blood side may therefore be a potential contributor to negative side effects, such as vascular calcification.

In conclusion, the choice of the DCa levels has major pathophysiologic effects and may be a silent effector in bone and vascular disease, as well as a contributor to hemodynamic stability during HD. The choice of the optimal DCa deserves a thoughtful process, taking into account the cardiovascular status, parameters of mineral metabolism, the concomitant use of drugs such as P-binders, cinacalcet or vitamin D analogues and the hemodynamic stability of the patient. Direct measurement of CaMB during dialysis is difficult to achieve on a daily clinical basis, but the introduction of kinetic models appears easier to implement [7, 8, 33, 35]. More research should focus on the optimal DCa taking into account the individual patient, making the treatment an optimal tailor-made treatment. In the meantime, the introduction of a DCa of 2.75 mEq/L would be a rational contribution to the current dialysis strategies.

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