Skeletal and cardiovascular consequences of a positive calcium balance during hemodialysis
Consequências esqueléticas e cardiovasculares de um balanço positivo de cálcio durante a hemodiálise

ABSTRACT

Patients on hemodialysis are exposed to calcium via the dialysate at least three times a week. Changes in serum calcium vary according to calcium mass transfer during dialysis, which is dependent on the gradient between serum and dialysate calcium concentration (d[Ca]) and the skeleton turnover status that alters the ability of bone to incorporate calcium. Although underappreciated, the d[Ca] can potentially cause positive calcium balance that leads to systemic organ damage, including associations with mortality, myocardial dysfunction, hemodynamic tolerability, vascular calcification, and arrhythmias. The pathophysiology of these adverse effects includes serum calcium changes, parathyroid hormone suppression, and vascular calcification through indirect and direct effects. Some organs are more susceptible to alterations in calcium homeostasis. In this review, we discuss the existing data and potential mechanisms linking the d[Ca] to calcium balance with consequent dysfunction of the skeleton, myocardium, and arteries.

Keywords: Chronic Kidney Disease-Mineral and Bone Disorder; Parathyroid; Calcium Transfer Mass; Vessels; Myocardium.

INTRODUCTION

Patients with end-stage kidney disease (ESKD) have increased morbidity and mortality; chronic kidney disease mineral bone disorder (CKD-MBD) is a consistent independent risk factor. Although calcium disturbances and treatments that alter serum calcium have been addressed in several reviews, the impact of a positive calcium balance during hemodialysis due to calcium dialysate content - d[Ca] - on this outcome is rarely considered.

Calcium is an essential mineral for the function of various organ systems through its impact on hormones and cell signaling. As a result, humans have a complex homeostatic system to maintain normal levels of calcium in the blood through regulation by multiple hormones acting on...
the intestine, parathyroid, kidneys, and bones. With evolution from fish to amphibians, the skeleton had to adapt because, compared to the ocean, the calcium content in land food and water is lower. Therefore, the skeleton became an organ that not only gave motility and strength to the body, but also served as a reservoir of calcium that can respond, even at its own expense, to maintain normal levels of ionized calcium. Calcium accounts for 1 to 2% of adult human weight, and over 99% is found in teeth and bones. The ratio of extracellular to intracellular calcium and the amount of calcium stored within the cells are tightly controlled.

This homeostasis is disrupted in patients with chronic kidney disease (CKD) due to disruption of normal homeostatic loops with kidney function decline, with compensatory changes in several hormones (parathyroid hormone - PTH, vitamin D, fibroblast growth factor 23 - FGF23). The abnormalities of CKD-MBD begin in some patients as early as eGFR of 70 mL/min/1.73m² and are almost universal when eGFR is < 30mL/min/1.73m². In the early 1970s, it was discovered that 1,25vitamin D levels were uniformly reduced, and calcium intestinal absorption was decreased in patients with CKD. The conclusion at that time was that patients with CKD were therefore in a negative calcium balance and thus would require calcitriol and/or calcium supplementation to enhance intestinal absorption and avoid hypocalcemia and secondary hyperparathyroidism. However, subsequent studies in patients with moderate CKD have shown that oral calcium carbonate supplementation or calcium-rich diet induce a positive overall calcium balance that might facilitate soft-tissue deposition of calcium salts. Furthermore, the discovery in the early 2000s that FGF23 inhibits calcitriol synthesis supports an attempt of the body to purposefully decrease intestinal calcium absorption, due to the marked reduction of calcium excretion with declining kidney function. These studies have led to the current concept that the decreased intestinal absorption is an appropriate adaptation to avoid positive calcium balance and its adverse consequences. The need for hemodialysis adds a new variable to this broken regulatory system as patients are exposed to an external calcium-rich solution (dialysate) during each dialysis treatment. The acute change in ionized calcium during dialysis can alter the balance between bone and serum calcium, further altering overall calcium balance (Figure 1). The purpose of this review is to examine the evidence supporting a pathologic role of a positive calcium balance on end organ damage in patients undergoing hemodialysis.

### Calcium Transport During Hemodialysis

Calcium balance during dialysis is defined as the net amount of calcium that is obtained (or lost) during a treatment. Briefly, this balance is determined by two factors: the calcium gradient and the ultrafiltration volume. Calcium gradient is defined by the difference between dialysate and serum calcium. The blood calcium is composed of three fractions: protein bound, complexed, and ionized. The ionized calcium is the active fraction representing ~50% of the total calcium. Only the ionized calcium and calcium complexed to small anions are transported across the dialyzer membrane, and the latter is only estimated and not usually measured. Albumin is the primary calcium-binding protein, but unfortunately, formulas...
estimating ionized calcium based on total calcium and albumin are inaccurate, particularly in dialysis patients. Calcium can also bind to phosphate and bicarbonate, and concentrations of both can change markedly during dialysis. Therefore, the difference between dialysate and the blood-free calcium times the total dialysate volume is the main component of the calcium mass balance during the dialysis and could be either negative or positive. Conversely, there will be always a negative balance of calcium due to the ultrafiltration volume. In other words, the patients will always loose a small amount of calcium when we prescribe a negative balance of water. However, this is a small component of the calcium balance during dialysis, and the calcium gradient predominates.

Usually, the concentration of total calcium in the extracellular compartment increases during dialysis and decreases between the sessions. In most studies, the use of d[Ca] of 1.5 or 1.75 mmol/L (3.0 or 3.5 mEq/L) leads to post-dialysis hypercalcemia and positive calcium balance. However, the actual calcium mass transfer is unpredictable due to 1) differences in the ionized calcium blood level, 2) differences in convective loss or calcium that varies depending on ultrafiltration, and 3) imprecise calculations of the delivered dialysate calcium. Finally, our work has shown that the increase in ionized calcium is greatest in the first 30 to 60 minutes and also depends on bone remodeling. Thus, not all patients will gain or lose calcium, or develop hyper- or hypocalcemia on the same d[Ca] concentration. However, as shown in Table 1, many studies based their conclusion on intradialytic calcium balance using only the serum calcium variation. Moreover, some studies have shown that changing sodium concentration in the dialysate will decrease the calcium concentration affecting the intradialytic calcium mass transfer.

Interestingly, the majority of the studies on intradialytic calcium balance was done on hemodialysis (Table 1). However, hemodiafiltration has been adopted by several centers, sometimes as the main modality of renal replacement therapy. In this case, water and fluid change through convection might reach 30 liters and certainly gains importance in comparison with the maximum 3-4 liters that are extracted in hemodialysis. Conversely, the diffusion process has a lower impact on the calcium balance when compared to hemodialysis. Studies on post-dilutional hemodiafiltration done in the 1990s show similar results on calcium balance to those on hemodialysis.

However, the use of pre-dilutional hemodiafiltration can be associated with a negative intradialytic calcium balance. Pieces of evidence of long-term effects of hemodiafiltration, however, are scarce in the literature. Argiles et al. in 1993 compared the effects of lowering d[Ca] to 1.25 mmol/L in 7 patients vs. 6 control patients using d[Ca] 1.5 mmol/L. Calcium carbonate oral intake was more than doubled in the low d[Ca] group. Total calcium, phosphate, and alkaline phosphatase were similar in both groups over the year. Basile et al. showed in 2001 that neither pre- nor post-dialysis systolic and diastolic blood pressures, pre-dialysis serum bicarbonate and pH, and pre-dialysis serum sodium, potassium, calcium, or phosphorus were significantly different when comparing hemodialysis and hemodiafiltration.

Another potential confounding factor for the intradialytic calcium balance is the use of citrate instead of acetate in the dialysate. It has been demonstrated that PTH decreases and ionized calcium increases using bicarbonate buffer, whereas acetate does the opposite, increasing PTH and decreasing serum calcium. Despite the intradialytic effect on calcium balance, it is important to recognize the potential acute effect of dialysis on serum calcium. It is plausible that acute changes in extracellular calcium may affect intracellular calcium concentration, which is a key signaling pathway for nearly every cell. In animal models of CKD, there is an increase in intracellular calcium concentration in multiple cell types. In cardiomyocytes, the increase is mediated by PTH through a process that includes both increased entry of calcium into cardiac myocytes and decreased exit of this ion from these cells. There is also an increase of basal intracellular calcium in vascular smooth muscle cells regardless of the PTH. Thus, acute extracellular changes in ionized calcium may alter cellular function by changing the gradient across the cell membrane, which in turn can alter intracellular calcium. For example, in cardiomyocytes and vascular smooth muscle cells, contraction occurs through the increase in cytoplasmic calcium that comes from the extracellular calcium and/or release from the sarcoplasmic reticulum and mitochondria. Conversely, cytosol calcium efflux leads to relaxation by energy-dependent with adenosine triphosphate (ATP) generation. Thus, acute changes in extracellular ionized calcium may alter the gradient across the cell membrane resulting in unwanted intracellular changes in calcium and cell dysfunction.
| Author     | Year | Method of dialysis/population | Buffer/Dialysate | Measurements                                                                 | Calcium Mass Transfer (CMT) |
|------------|------|-------------------------------|------------------|----------------------------------------------------------------------------|----------------------------|
| Ogden      | 1966 | HD with tank and coil; 5h; N = ? / 25 sessions | Acetate/coil dialyzer | Estimated using differences between initial and final serum tCa | -d[Ca] of 1.125 mmol/L = -124 mg <br> -d[Ca] of 1.375 mmol/L = 0 mg <br> -d[Ca] of 1.75 mmol/L = +426 mg |
| Wing       | 1968 | HD with tank and Kil; 12h; N = 1, 10 sessions | Acetate/Kil dialyzer | Measurement of tCa in the total volume of dialysate | -Several d[Ca]s, from 0.738 to 1.988 mmol/L <br> -CMT from -1,114 to +740 mg |
| Goldsmith  | 1971 | HD with tank and Kil; 6h; N = 5 | Acetate | Measurement of tCa and 45Ca in samples of dialysate | -Formula proposta -Proposed Formula - Net gain [mg/min] = 0.108 + 0.623 x calcium gradient [mg/ml] |
| Strong     | 1971 | HD with tank and Kil; 3-4h; N = 13 | Acetate | Measurement of tCa, 47Ca and 45Ca in samples of dialysate | -d[Ca] of 1.475 mmol/L = 0 mg <br> -d[Ca] of 1.725 mmol/L = +91 mg <br> -d[Ca] of 1.975 mmol/L = +240 mg |
| Skrabal    | 1974 | HD with tank and coil; 8h; N = 3 | Acetate | Measurement of tCa in samples of dialysate | -d[Ca] of 1.5 mmol/L = +72 mg <br> -d[Ca] of 2 mmol/L = +240 mg |
| Carney     | 1985 | HD | Bicarbonate | ? | -d[Ca] of 1.65 mmol/L = from -66 to +72 mg |
| Hou        | 1991 | HD; 4h; N = 7; Baxter SPS 550 | Bicarbonate | Measurement of tCa in samples of dialysate | -d[Ca] of 0.75 mmol/L = -231 mg <br> -d[Ca] of 1.25 mmol/L = 0 mg <br> -d[Ca] of 1.75 mmol/L = +879 mg |
| Argilès    | 1993 | Post-dilutional HDF; 3h; N = 9 | Bicarbonate | Measurement of iCa in samples of dialysate. | -No calculation of CMT. Assumption that CMT is neutral with d[Ca] of 1.25 mmol/L, slightly + with 1.5 mmol/L, and significantly + with 1.75 mmol/L |
| Malbert    | 1994 | Post-dilutional HDF; 4h; N = 7 | Bicarbonate | Measurement of tCa in the total volume of dialysate | -d[Ca] of 1.25 mmol/L = -44.8 mg for infusion rate = 2.5/l/h and -56.8 mg for infusion rate = 5/l/h <br> -d[Ca] of 1.5 mmol/L = -23.6 mg for infusion rate = 2.5/l/h and -22.8 mg for infusion rate = 5/l/h <br> -d[Ca] of 1.75 mmol/L = -11.2 mg for infusion rate = 2.5/l/h and -13.2 mg for infusion rate = 5/l/h |
| Argilès    | 1995 | Post-dilutional HDF; 4h; N = 14, proportion machine | Bicarbonate | Measurement of iCa and tCa in samples of dialysate. | Using iCa: -d[Ca] of 1.25 mmol/L = neutral; d[Ca] of 1.5 mmol/L = positive <br> Using tCa: -d[Ca] of 1.25 mmol/L = negative; d[Ca] of 1.5 mmol/L = neutral |
| Fabrizi    | 1996 | HD; 4h; N = 6, proportion machine | Bicarbonate | Measurement of iCa in samples of dialysate | -d[Ca] of 1.25 mmol/L = -6 mg <br> -d[Ca] of 1.75 mmol/L = +308 mg |
| Ding       | 2002 | Pre-dilution HDF, post-dilution HDF and acetate free HD/N = 12 | Bicarbonate/Citrate | Measurement of blood iCa and tCa | -CMT not measured <br> -use of different d[Ca] for HDF and acetate free HD |
| Study | Year | Methodology | Type of Calcium | Details |
|-------|------|-------------|-----------------|---------|
| Al-Hejaili | 2003 | HD, 2, 4 and 6h; N = 14 | Bicarbonate | Measurement of tCa in the total volume of dialysate: -d[Ca] of 1.25 mmol/L = -25 mg in 2h; -0.6 mg in 4 h and – 82 mg in 6h; -d[Ca] of 1.75 mmol/L = + 43 mg in 2h; 96 in 6h |
| Sigrist | 2006 | HD; 4h; N = 52 | Bicarbonate | Measurement of tCa in proportional samples of dialysate: -d[Ca] of 1.25 mmol/L = -187 mg (range: - 486 - + 784 mg) |
| Karohl | 2010 | HD, 4h, N = 23, Genius Hemodialysis system | Bicarbonate | Measurement of tCa in a proportional sample of dialysate: -d[Ca] of 1.25 mmol/L = -187 mg (range: - 486 - + 784 mg) |
| Basile | 2011 | HD, 4 and 8h; N = 11; Genius Hemodialysis system | Bicarbonate | Measurement of iCa in a proportional sample of dialysate: -d[Ca] of 1.0 mmol/L = -492 mg; -d[Ca] of 1.25 mmol/L = -468 mg; -d[Ca] of 1.5 mmol/L = -46 mg; -d[Ca] of 1.75 mmol/L = + 268 mg |
| Movili E | 2011 | HD switched to HDF (N=30 vs 35 control) | Bicarbonate | Effect of 6 months of HDF on serum Ca, P and PTH: -CMT not measured |
| Bosticardo | 2012 | HD; 4h; N = 22 | Bicarbonate | Measurement of iCa in proportional samples of dialysate: -d[Ca] of 1.5 mmol/L; 4h = + 285 mg; 8h = + 298 mg |
| Grundstrom | 2013 | HD N=9/HDF N=11 | Bicarbonate/Citrate | Measurement of iCa in samples of blood: -CMT not measured |
| Safranek | 2015 | HD 4h, N=80 and Post-dilutional HDF N=46 | Bicarbonate/Citrate | Measurement of iCa and tCa in samples of blood: -CMT not measured |
| Bacchetta | 2015 | HDF; 4h; N=28 children | Bicarbonate | Measurement of iCa and tCa in samples of blood: -CMT not measured |

Using iCa:
- d[Ca] of 1.25 mmol/L = +97 ± 128 mg
- d[Ca] of 1.375 mmol/L = +187 ± 146 mg
- d[Ca] of 1.5 mmol/L = +326 ± 253 mg

Using tCa:
- d[Ca] of 1.25 mmol/L = +75 ± 122 mg
- d[Ca] of 1.375 mmol/L = +182 ± 125 mg
- d[Ca] of 1.5 mmol/L = +293 ± 228 mg

Citrate dialysis fluid resulted in lower post-dialysis plasma iCa (1.10 mM vs. 1.27 mM)

Decrease of tCa and iCa with D[Ca] 1.25 and no change with D[Ca] 1.5 mmol/L
- Increasing bicarbonate and/or decreasing Na requested in the dialysate decreases calcium extraction from the acid preparation
The role of the skeleton in calcium mass transfer

Several studies have shown that a lower $d[Ca]$ acutely increases serum PTH resulting in increased bone turnover. It was previously thought that the variation in serum calcium concentration during dialysis could be a good predictor of calcium mass transfer from the dialysis procedure. Based on this simplistic equation, authors had determined that $d[Ca]$ of 1.25, 1.5, and 1.75 mmol/L would lead to a negative, neutral and positive calcium balance, respectively, with variable effects on bone turnover. However, calcium balance during hemodialysis is actually hard to predict due to the variables described above, and can be either positive or negative with the same $d[Ca]$ in a given patient. Nevertheless, in general, positive balance is likely when using high (1.75 mmol/L) $d[Ca]$ compared to a low 1.25 mmol/L $d[Ca]$.  

One of the confounding factors for the poor accuracy of serum calcium to predict calcium balance is the skeleton. Bone is a reservoir of an exchangeable 300 mg/day of calcium. Almost 20 years ago, Talmage et al. hypothesized that PTH not only stimulates osteoclast-mediated bone resorption, but also increases the content of some bone surface calcium binding proteins, such as osteocalcin, that could act as calcium buffers. In other words, PTH would increase the amount of osteocalcin in the bone surface, increasing the capacity of the skeleton to acutely donate or retain calcium during dialysis, depending on acute changes in blood calcium. More than 20 years ago, Kurz et al., using double radiolabeled calcium, showed that the acute bone calcium uptake was higher in high turnover bone disease compared to either mixed uremic osteodystrophy or low turnover bone on a non-dialysis day. Therefore, the skeleton determines not only the exchangeable calcium pool during dialysis but also the pre-dialysis serum calcium through its response to PTH. Indeed, recent
studies have proven that calcium balance also varies according to bone turnover status. We and others have shown that calcium balance varies from negative 1500 to positive 800 mg using the same d[Ca] of 1.25 mmol/L.

Our group has demonstrated the association between bone remodeling markers and calcium mass transfer during a conventional hemodialysis. We studied 23 patients dialyzed using a d[Ca] of 1.0, 1.25, 1.5, and 1.75 mmol/L, in which the mean ± SD and range of calcium removal was -578, -468, 46, and 405 mg, respectively. Multivariate analysis showed that calcium balance was dependent on calcium gradient, PTH, and osteocalcin. Bone remodeling, however, is hard to predict when based only on biomarkers. The ideal study design to evaluate the influence of bone remodeling state on calcium balance would be a repeated analysis in the same patient with different bone turnovers, and maintaining other biases unchanged, i.e., ultrafiltration volume and d[Ca]. We conducted such a study, examining calcium mass transfer in the same patients before parathyroidectomy (PTX), during the first month after surgery in the hungry bone phase, and after surgery when blood calcium stabilized. We confirmed a wide variation of calcium mass transfer during hemodialysis according to each phase (before PTX, hungry bone, and late after PTX) and each d[Ca] used (1.25 vs. 1.5 vs. 1.75 mmol/L). Even with no difference in the ultrafiltration volume, calcium mass transfer varied among phases and among d[Ca] used, supporting our hypothesis of the importance of bone turnover. (Figure 2)

Therefore, the skeleton is a key determinant in net calcium gain or loss during dialysis, and is an important consideration when prescribing the optimal dialysate calcium.

Figure 2. The challenge to predict calcium balance during dialysis based on pre-dialysis serum calcium. Although there is a trend to increase the calcium influx when using higher d[Ca], there is a significant inter-individual variation. Also, there is an intra-individual variation when we compare the same patient in 3 distinct clinical situations: before parathyroidectomy, during hungry bone phase, and later after parathyroidectomy. Calcium gradient and mass transfer using d[Ca] of 1.25mmol/L (blue bars), 1.5mmol/L (red bars), and 1.75 mmol/L (green bars). Data obtained from Goldenstein et al.
The leading cause of death is cardiovascular events. Alterations in the d[Ca] may be a plausible mechanism to stabilize blood pressure/hemodynamics, myocardial function, hemodynamics, and reduce arrhythmias, especially during and immediately after the dialysis treatment. The effect of d[Ca] on myocardial perfusion has been studied by a number of methods. Myocardial stunning is common during dialysis, and it can be minimized by the use of a cool dialysate and the reduction of the ultrafiltration rate, which can be achieved by changing to short daily or long nocturnal hemodialysis sessions. Diastolic dysfunction, an independent predictor of mortality in patients on dialysis, involves abnormal left ventricular relaxation, filling, and distensibility. As coronary blood flow is greater during diastole, diastolic dysfunction may lead to the reduction of coronary perfusion, which may lead to subendocardial ischemia and systolic dysfunction.

Using echocardiography, one study measured diastolic function in hemodialysis with no ultrafiltration on a 1.75 mmol/L d[Ca], finding no impairment in diastolic function despite an increase in ionized calcium. However, two other studies using calcium gluconate infusion or a high d[Ca] of 1.75 mmol/L both found impaired diastolic relaxation. Therefore, studies suggest that higher calcium dialysate may worsen ventricular relaxation assessed by echocardiography.

Recently, our group used a more sensitive method, two dimensional speckle imaging with strain analysis, to evaluate the impact of d[Ca] on myocardial performance during hemodialysis. We found hypercalcemia (11.5 ± 0.8 mg/dL) after hemodialysis using d[Ca] of 1.75 mmol/L and improved hemodynamic stability in terms of blood pressure. However, the global longitudinal strain (GLS) was worse during the last hour of hemodialysis compared to baseline (p < 0.001). In addition, the GLS was worse with d[Ca] of 1.75 than 1.25 mmol/L (-16.1 ± 2.6% vs. -17.3 ± 2.9%, respectively; p < 0.001). Multiple linear regression showed that independent risk factors for GLS were transferrin, c-reactive protein, baseline GLS, weight loss during hemodialysis, and post dialysis serum calcium.

Previous studies have shown an increased calcium-induced myocardial contractility when a d[Ca] of 1.75 mmol/L was employed. However, one of these studies was performed in 1984 and included only eight patients using three different d[Ca] to evaluate the left ventricular contractility by two-dimensional echocardiography. Authors concluded that the increase of ionized calcium after dialysis was associated with an improvement of contractility. Other authors four years later included seven patients and tested 3 different d[Ca]. Left ventricular contractility was assessed using the relation between left ventricular end-systolic wall stress and myocardial systolic performance. They concluded that high d[Ca] had a positive impact of myocardial performance. A recent study has evaluated cardiac function in a Langendorff-like system of a zebrafish. By manipulating the calcium concentration of the perfusion buffer, authors surprisingly found that the ejection fraction initially increased along with the increase in calcium concentration, similarly to previously mentioned studies, and then decreased. Although the experimental scenario is unlike clinical practice, this finding should raise alert about the deleterious effect of high d[Ca]. There is no doubt that calcium is imperative to ventricular contraction. These inconsistent findings suggest that calcium is indeed important for effective myocardial contraction in an almost direct relationship, although hypercalcemia can impair ventricular function.

Figure 3. Bull’s Eye diagram of four-chamber view and peak longitudinal strain values of all left ventricular segments. The diagram represents the analysis of four-chamber, two-chamber, and left ventricular long axis view, before dialysis (baseline) and at the peak of dialysis (last hour) using d[Ca] of 1.25 mmol/L and 1.75 mmol/L in the same patient, one-week apart. The color-coded map denotes values of peak systolic strain of each segment, with lighter color meaning worse left systolic ventricular dysfunction, which was evident with dialysis, and worse using d[Ca] 1.75 mmol/L.
Positive calcium balance and/or hypercalcemia are involved in the pathogenesis of arterial calcification. VSMC move from a contractile to synthetic phenotype, a prerequisite for de-differentiation. In rats with CKD, freshly isolated VSMC from aorta have increased intracellular calcium concentration, indicative of the synthetic state. These cells then upregulate RUNX2 to become osteo-chondrocytic-like cells in the presence of uremic serum. Shanahan and colleagues demonstrated that calcium induces release of matrix vesicles and increased calcification independently and synergistically with phosphate in cultured VSMC. Giachelli’s group also demonstrated that calcium-induced calcification was synergistic with hyperphosphatemia. Furthermore, they demonstrated that incubating VSMC with high calcium media led to upregulation of Pit-1, a sodium-phosphate transporter important in the upregulation of RUNX. In vivo, calcium containing phosphate binders induce arterial calcification in 5/6th nephrectomy rats, Cy/+ model of CKD, and the LDLR/- high-fat-fed mice with CKD despite lower levels of serum phosphate. In our Cy/+ rat model of progressive kidney disease, we treated rats with advanced CKD with calcium administered in drinking water, calcimimetic R-568, and R-568 plus calcium versus no treatment. Treatment with calcium in the drinking water led to increased thoracic aorta, heart, and aortic valve calcification regardless of the serum level of calcium, indicating positive calcium exposure/balance can induce arterial calcification regardless of calcium blood levels. The calcium treatment led to an even greater calcification than observed with hyperphosphatemia and normal calcium levels. Thus, hypercalcemia, or positive calcium balance even without hypercalcemia, can directly induce calcification in vitro and in vivo.

In patients receiving hemodialysis, most randomized trials comparing calcium-based phosphate binders, compared to non-calcium binders, show greater progression of coronary artery calcification. However, studies examining the role of calcium load from dialysate calcium are limited. A small study compared dialyzed patients against three acute variations of calcium concentrations and found increased carotid-femoral and carotid-radial pulse wave velocity (PWV; a measure of increased stiffness) with higher dialysate calcium. Another small study randomized patients on nocturnal dialysis to low calcium dialysate (1.3 mmol/L, n = 24) or high calcium dialysate (1.6 or 1.75 mmol/L, n = 26) and found no difference in abdominal aorta calcification by CT over one year.
However, Ok and colleagues (17) conducted a large randomized trial in patients on thrice weekly HD with intact parathyroid hormone levels ≤ 300 randomized to 1.25-mmol/L Ca dialysate (n = 212) or 1.75-mmol/L Ca dialysate (n = 213). The results showed a significant increase in coronary artery calcification in the patients randomized to 1.75 mmol/L Ca dialysate compared to the lower dialysate calcium. Importantly, hyperphosphatemia also increased coronary artery calcification, and the combination of hyperphosphatemia and high calcium dialysate was additive in inducing increased coronary artery calcification. Thus, increased calcium dialysate, especially in the setting of hyperphosphatemia, appears to increase arterial calcification in hemodialysis patients, similar to observations from in vitro VSMC cultures and in vivo in rodent models of CKD.

**Conclusion**

The d[Ca] can cause acute hypercalcemia in a given patient, depending on ultrafiltration volume and bone turnover status. However, the role of d[Ca] causing a positive calcium balance as a primary cause of systemic organ damage is not well appreciated. This review addressed potential associations between d[Ca] and systemic changes in the skeleton, myocardial, and vessels. The best d[Ca] remains unknown as both low and high d[Ca] can improve or deteriorate organ function. As an example, while low d[Ca] can be a good choice for patients with adynamic bone disease to avoid vascular calcification, it can also induce hypocalcemia and stimulate PTH secretion, leading to high risk of arrhythmias and cardiac arrest. On the other hand, high d[Ca] can lead to better hemodynamic stability, although this may increase the risk of calcification, suppress the PTH secretion, and cause ventricular dysfunction during hemodialysis.

It is difficult to distinguish between the direct effect of d[Ca] versus indirect effect of d[Ca] on hypercalcemia. However, since d[Ca] is a major determinant of serum calcium levels, or at least acute changes during dialysis, there is a need for more research to fully elucidate the impact of d[Ca] on systemic organ damage and to establish a direct cause-effect relationship. However, the accumulated data to date does support that central pumping of specific d[Ca] in outpatient dialysis units is not a good practice, as one size does not fit all.

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**Author's contribution**

All authors participated in the conception, writing, revision and approval of the final version of the manuscript.

**Conflict of interest**

Nothing to declare.

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