The ups and downs of dialysate calcium concentration in haemodialysis patients

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The absence of consensus on what should be the ideal dialysate calcium (DCa) concentration in haemodialysis patients is in part explained by the continuously changing therapeutic practice, but also on the scanty evidence that has been produced on this topic. The lack of consistent studies in this field is in part due to a number of methodological limitations for the assessment of both the global external and dialysis calcium balance. Some recent studies, one of which was published in the present issue of the NDT Journal, have added some important information in this field. The main aim of the present editorial is to comment on these recent contributions and also to focus on the foremost limitations and difficulties in the execution of calcium balance studies and their interpretation.

The question of what should be the ideal dialysate calcium (DCa) concentration has troubled nephrologists from the earliest days of the dialysis history and still troubles them.

The persistence of uncertainties concerning this issue is in part due to the continuously changing scenario in the therapeutic approach to the control of secondary hyperparathyroidism (SHP) and of the related mineral metabolism changes. In fact, at the very beginning of the dialysis history, a DCa close to the physiological concentration of ionized calcium (iCa) in the blood (1.25 mmol/L) was used. At that time, no effective drug was available for the control of SHP and consequently hypocalcaemia and severe SHP were almost invariably observed. To overcome these problems, in the following years, a DCa of 1.75 mmol/L was recommended [1], which was used for a long time, even after calcium-based phosphate binders (PiBs) almost completely replaced aluminum hydroxide and when calcitriol and other potent vitamin D analogues became available. This translated into an increased extra- and intra-dialytic burden of calcium, an over-suppression of parathyroid hormone (PTH) with a consequent increased prevalence of adynamic bone disease (ABD) and probably an increased risk of the occurrence of vascular calcifications. The initial awareness of a possible unacceptable positive calcium balance drove nephrologists to lower again the DCa content to 1.50 mmol/L, which was the most widely used concentration in the late nineties. Furthermore, this awareness developed even more after the K/DOQI guidelines, edited in 2003, recommended going back to an even lower DCa (1.25 mmol/L), in association with the suggestion of using a limited maximal dose of calcium-based PiBs [2].

However, also this position continues to date to be the object of conflicting opinions which hamper the achievement of a consensus on this matter [3–6].

It is also worth stressing that for the most part, this controversy is also justified by the dearth of clinical and/or experimental evidence needed for filling the large knowledge gaps concerning many critical aspects related to both the global and the dialysis calcium balance.

Very recently, some papers (one of which has been published in the present issue of NDT) added some additional and, in my opinion, important points in this much debated subject [7–9]. In light of these recent studies, I would like to briefly comment on some of the main unsolved questions concerning calcium balance in haemodialysis patients, considered as both the global external and the dialysis-limited balance.

The global external calcium balance (GECaB) can be simply defined as the algebraic sum of the calcium intake minus calcium losses (GECaB in healthy people is broadly described in Figure 1). In a healthy and metabolically stable person, with the assumption that the net calcium movement from and to the internal compartments (the bone-exchangeable pool, mineralized bone compartments, other internal miscible pools, intracellular stores, etc.) is null, GECaB is expected to be close to 0, with the urinary calcium excretion matching the net intestinal calcium absorption (ICAa) (dietary minus fecal calcium amount). However, this basic assumption is not altogether true since these as yet not completely defined ‘internal calcium compartments’ are far from being in a constant steady-state condition, i.e. the inward and outward transfers do not completely match each other at any given time. Hence, for a precise assessment of the real GECaB and the net ICaA we should measure the amount of calcium of the diet and the calcium losses through the
Fecal, urinary and, less importantly, cutaneous routes. Though this might appear to be simple, the assessment of all these components of the GECaB is undermined by a number of complexities and limitations, which have been addressed in recent papers [10, 11]. I would like just to limit myself to commenting on the most relevant critical aspects which are related to the assessment of the fecal calcium losses. First, the accomplishment of a complete collection of feces is not an easy task, since the wide intra- and inter-individual differences in the transit time of the alimentary bolus through the intestinal tract makes it very difficult to match the fecal output with the corresponding dietary intake. This means that we have to extend the stool collection period over a prolonged and not precisely defined time, which can be quite different from one subject to another. This implies a complicated and often unacceptable involvement of patients and medical staff. Second, the measurement of calcium concentration in the stools is burdened by a number of analytical complexities due to the poorly homogenous fecal matrix which necessitates a complicated pre-analytical treatment. Third, the assessment of the dietary calcium content is usually derived from the recorded dietary diaries and is more frequently calculated and not measured through dietary tables. In addition to the possible inaccuracies of such methods, it should also be taken into account that the bioavailability of dietary calcium is quite variable depending on the type of the associated anions which are not fully assessed through the available dietary tables (e.g. phytate and oxalate reduce calcium bioavailability more than carbonate or gluconate).

If these are the main difficulties in assessing GECaB in healthy individuals, even more problematic is its assessment in chronic kidney disease (CKD) patients. In fact, the progressive reduction of urinary calcium excretion observed particularly in the most advanced stages of CKD has been ascribed to a consensual reduction of ICaA, in turn due to the reduced calcitriol levels. However, the scanty studies assessing this aspect are largely based on radioisotope techniques [12–14] which, in addition to being expensive, explore such a complex kinetic status just on a one-day basis which could not be extrapolated in the long term, given the functional variability of the calcium pools over time. The few older studies addressing this topic by a direct measurement of the ICaA partially contradicted the common belief showing that, under basal conditions, the ICaA in CKD patients mostly depends on the calcium availability in the intestinal tract, almost in the same way and to the same extent as in healthy individuals [15, 16]. Furthermore, another dated study showed that the ICaA can be also modified by dialysis treatment [17]. In addition, there is an ever more increasing awareness that CKD patients have a greater expansion of some of the internal calcium pools, particularly due to an exceedingly high prevalence of calcifications in the soft tissue, whose unknown kinetics characteristics might contribute to an unpredictable extent to the internal calcium distribution. Even more limited is the information on the potential effects on the different components of calcium balance by the drugs frequently used in CKD patients for the control of SHP (vitamin D metabolites and analogues, PiBs, calcimimetics, etc).

In this scenario, lacking hard evidence and full of uncertain opinions, the recent paper of Spiegel and Brady [8] added some important information in the field. In this study, using a crossover design, the global calcium balance was evaluated in six patients with stage 3 or 4 CKD and in six control subjects both on 800 mg and on 2000 mg elemental calcium per day. The main conclusions were that increasing calcium intake induces a positive calcium balance in healthy subjects as well as in CKD patients; these changes were apparently independent...
of calcitriol and PTH levels, since both hormones decreased; the changes in calcium balance were not associated with any change in calcium concentration, stressing the concept that calcium concentration cannot be considered a reliable index of calcium balance. It is worth stressing also that this study, as with the few other balance studies, are burdened by a number of methodological imprecisions, particularly when performed in a limited number of subjects. Despite these limitations, this study has the advantage of being one of the few studies which evaluated calcium content in the diet, stools and urine, reinforcing the conclusions of a quite similar study published four decades before [16].

It is also worth underlining that the calcium balance studies alone, though giving at best an exact estimation of the net calcium amount entering the body pools, cannot provide any information on whether the retained calcium would reach the right (bone) or the wrong place (soft tissues), particularly in the case of CKD patients.

Once more, the main lesson we learn from these papers is that, in the absence of comprehensive balance studies, which unfortunately are very difficult to be performed, any statement on GECaB might turn out to be unfounded and needs to be backed up by hard evidence.

When CKD progresses up to end-stage renal disease (ESRD), the contribution of urinary output to the calcium balance becomes negligible. So, in patients on dialysis treatment, where the residual renal function is null or close to null, the GECaB, in addition to the contribution of the intestinal tract, depends also on the calcium mass transfer (CaMT) from and toward the dialysate fluid, during the dialysis treatment, which is usually defined as the ‘dialysis calcium balance’ (DCaB). Though the data regarding the dialysis CaMT are once again scanty and offer incomplete information, it is widely accepted that CaMT is mainly determined by the gradient between the dialysate and serum calcium concentrations and on the ultrafiltration (UF) volume [18]. The few studies, which evaluated the DCaB with different DCa concentrations, came to the conclusion that CaMT is substantially neutral when a DCa concentration of 1.25 mmol/L is used, while DCaB is consistently negative or positive when DCa is <1.25 or ≥1.5 mmol/L, respectively [19, 20]. Other authors evaluated the CaMT during dialysis techniques characterized by higher UF rates than traditional haemodialysis (haemodiafiltration), drawing the conclusion that a DCa level >1.25 mmol/L is needed for providing a neutral DCaB [21–23].

Partially at variance with these results, Gotch et al. revisited this topic with a purely theoretical approach, coming to the conclusion that 1.25 mmol/L might be even too high a calcium dialysate concentration to avoid a positive calcium balance [6].

It is worth underlining that most studies directly assessing DCaB suffer from some technical limitations. In fact, given the relatively low DCa concentration and the exceedingly high volume of total discharged dialysate, even a low inaccuracy in the analytical method might translate into a critically different calculation of global CaMT. Furthermore, the DCa concentration has been found to be relatively unstable and variable, adding further inaccuracy in the calculation of DCaB [20].

On the other hand, the theoretical approach used by Gotch et al. [6, 24], though formally correct, relies on a number of theoretical assumptions. Limiting ourselves to quote only the most relevant two: first, the ICaA was extrapolated from the results of previous studies performed in healthy people and evaluated only indirectly, based on the urinary excretion of calcium; second, the distribution pools of calcium were taken as constant during the dialysis treatment, which is probably not a plausible situation in a condition which is characterized by rapid electrolyte and hormonal changes.

In any case, whatever the calcium concentration associated to a neutral CaMT is, the real point, which is far from being agreed concerns which DCaB should be considered as ideal. There are at least two main different currents of thoughts on this topic [3–6]. The first opinion is that DCaB should be basically null, since, when negative, a reduction of serum calcium levels is expected, which might stimulate PTH secretion, consequently inducing a calcium resorption from bone; on the other hand, in the case of a positive DCaB, the consequent calcium overload might negatively impact on the vascular calcification process. The alternative point of view is that, taking for granted a basically positive extra-dialysis calcium balance, particularly when vitamin D metabolites and/or calcium-based PiBs are used, a negative DCaB should be desirable for limiting the total calcium burden.

In this issue of the NDT Journal, Jean et al. [9] look at this critical topic. The authors evaluated the changes in PTH, calcium and phosphorus serum levels in 78 haemodialysis patients submitted to a shift from lower to higher DCa concentrations (from 1.25 to 1.50 or from 1.50 to 1.75 mmol/L) or vice versa (from 1.75 to 1.50 or from 1.50 to 1.25 mmol/L). The shift from lower to higher DCa concentrations were dictated by PTH >300 pg/mL or hypocalcaemia (not defined), while the presence of PTH <150 pg/mL or of relative hypercalcaemia (>2.50 mmol/L) prompted doctors to decrease the DCa concentration. The final result of the shift from lower to higher DCa was a substantial reduction of PTH associated with increased calcium and reduced phosphorus levels, while the opposite shift in DCa induced a significant stimulation of PTH secretion, together with a reduction of calcium and an increase of phosphorus levels. The results of this study reinforce many opinions shared by most nephrologists.

First, there is no DCa concentration ideal for all and its choice should be made on a customized basis. Second, the use of higher DCa concentrations can substantially improve the control of SHP in a very simple and inexpensive way. Third, a lower DCa might effectively stimulate PTH secretion and hence the bone metabolism, suggesting its usefulness under conditions of suspected or proven ABD.

Though many suggestions proposed by this study can be sharable, some considerations are worth doing in order to critically accept this advice. A first point to be discussed concerns the indication to increase DCa for correcting hypocalcaemia. In fact, when plasma calcium levels are lower, the dialysate-calcium gradient is greater and a more positive DCaB is expected and hence there is a minor need for increasing DCa for obtaining a positive DCaB.
Furthermore, it may be questionable to correct hypocalcemia, particularly if asymptomatic, by a direct intravenous calcium load, instead of handling the doses of vitamin D and/or calcimimetics and/or calcium-based PiBs.

A second point worth addressing is related to the possible dissociation between the changes in calcium concentration and CaMT. In a very recent study, even though carried out using a not widespread dialysis system (GENIUS single-pass batch dialysis system by Fresenius), Basile et al. [7] assessed the dialysis calcium balance in 22 patients using three different DCa concentrations (1.25, 1.325 and 1.50 mmol/L) with a cross-over design. Very interestingly these authors found that, notwithstanding that DCAb was positive with all three DCa concentrations, though to a different extent, the use of 1.25 mmol/L DCA induced a reduction in plasma iCa concentration and concomitant increase in PTH, while the other two DCa concentrations increased plasma water iCa with a concomitant inhibition of PTH levels. These results reinforce the opinion that the movements of calcium among the different pools probably do not remain constant during dialysis treatment, potentially affecting in an opposite direction the calcium concentration in the extracellular fluids and in the miscible compartments. So, only the reduction of iCa and the PTH stimulation cannot exclude the presence of a positive CaMT toward the internal pool.

A third aspect, strictly linked to the previous point, is the question whether there is a real advantage in correcting SHP through an increased DCAb. In fact, even if we would decide to reduce PTH levels through an increased calcium load, the main problem is whether it is worth choosing an unphysiologic route such as the intravenous route for achieving this result. Supporting concern on such a choice, the results from the DOPPS study showed that higher DCA, though associated with a lower rate of parathyroidectomies, was also found to be matched by an increased risk of mortality. However, we need even more consistent data on global external and dialysis calcium balance, in the absence of which our decisions will still remain mostly bound to suggestions and opinions.

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(See related article by Jean et al. Biological impact of targeted dialysate calcium changes in haemodialysis patients: the key role of parathyroid hormone. Nephrol Dial Transplant 2013; 28: 176–182.)

References

Targeting B-cells in lupus nephritis: should cautious optimism remain?

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Many in the lupus community anticipated that monoclonal antibody therapy targeting B-cells would dramatically alter the treatment of lupus nephritis (LN). Rituximab was supposed to be the long sought-after breakthrough in a field that had only incrementally advanced, substituting mycophenolate mofetil (MMF) for cyclophosphamide but with no substantive improvement in complete remission rates [1]. Anticipation turned to disappointment when LUNAR (Lupus Nephritis Assessment with Rituximab), a large, placebo-controlled randomized clinical trial, did not show that rituximab added to MMF and corticosteroids did better than placebo added to MMF and corticosteroids [2]. Much of this disappointment was because of the positive published experience with off-label use of rituximab for refractory LN, generally consisting of case reports, registries or small series. These studies are reviewed in the current issue of the journal by Weidenbusch et al. [3]. The authors make a compelling argument that perhaps rituximab has a niche for refractory LN, despite the LUNAR results. They do so while acknowledging that the evidence favoring rituximab in refractory LN is difficult to interpret, because the supporting studies are not controlled or randomized and are subject to the publication bias of positive outcomes. Furthermore, in these studies the definition of refractory is not standard, the dosing of rituximab is not consistent, and other immunosuppressive agents were often used concomitantly. That said, the existing evidence has generated enough suspicion of efficacy that it would be worthwhile to undertake a controlled trial of rituximab in LN unresponsive to multiple courses of therapy and/or multiple treatment types.

Legitimate objections to a trial of rituximab in refractory LN may be raised. It is counterintuitive to expect rituximab to be beneficial in disease that has proven very difficult to treat, when it did not succeed in incident disease (LUNAR had many newly diagnosed patients), which could be expected to be more responsive to therapy. While there is no clear-cut answer, one possibility is suggested by the mechanisms of action of rituximab. This antibody is very good at depleting circulating B-cells, but marginal zone B-cells, germinal center B-cells and peritoneal B-cells do not deplete well [4]. These protected cells may contribute to ongoing pathogenic events in LN. It is conceivable that after several rounds of cytotoxic therapy in refractory LN, sequestered...