Seminars in Dialysis

# Should Dialysate Calcium be Individualized?

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**ABSTRACT**

The growing interest in a personalized choice of dialysate calcium concentration faces some important unsolved questions. First, the desired aims to be achieved should be clarified, as different d-Ca concentrations might differentially impact dialysis calcium balance and serum calcium concentration. A second point to be addressed is how to achieve the desired goals; the kinetics of calcium during dialysis treatment are complex. This is not an easy task and probably only an automatic device able to read serum calcium concentration in real-time and adjust d-Ca to it might supply an effective method for individualizing d-Ca. Finally, it is not even clear whether individualizing d-Ca is worth doing; cost-effectiveness studies might give some further insights into this intricate issue.

The "boom" of interest in individualized medicine in recent years (over 5500 publications quoted in PubMed in the last 5 years) is based on the growing awareness of the extreme individual variability in the clinical expression of any disease, which cannot be addressed by a homogeneously repetitive therapeutic approach. This trend is also true for dialysis patients, with a growing belief in the need for individualizing dialysis treatments. In particular, the question of what the ideal dialysate calcium should be has been one of the most discussed issues among nephrologists in the past and is still matter of debate.

Much of the debate on this topic is related to the intricate relationships between the dialysis and the global calcium balance, due to the complex and not completely defined role of the dietary calcium content, intestinal absorption and secretion and the not-yet-defined kinetics of the different intra-corporeal pools of calcium. Furthermore, as dialysis practice has evolved, new drugs (vitamin D analogs, calcimimetics, calcium-containing and calcium-free phosphate binders) have been introduced into clinical practice for managing mineral-bone disease (CKD-MBD). These new therapeutic tools have variable and, to a certain extent, opposing effects on calcium-related metabolic variables, and have further complicated the scenario. Many of these unsolved considerations have been addressed in a recent paper (1).

In the present editorial, we discuss some specific aspects related to the individualization of dialysate Ca (d-Ca), primarily focusing on three main points: the possible aim(s) for a personalized d-Ca; the way to achieve the desired goals; the advantages (if any) of individualizing d-Ca.

## The Aims of Individualizing d-Ca

For the individualization of any therapeutic approach, one should have the desired goal(s) clearly in mind.

As d-Ca is the main variable affecting dialysis calcium balance (DCaB) (2), the individualization of d-Ca might first be aimed to obtain a desired null, positive or negative calcium balance in a patient. There is still much debate on what the ideal DCaB should be (3,4). The K-DOQI guidelines suggest that a negative or null DCaB might be more advisable than a positive one (5).

Noting the spontaneous negative or null *intestinal* calcium balance (ICaB) in patients with CKD, some nephrologists support a positive DCaB, believing that it can guarantee a better control of PTH levels and a more healthy bone. Other nephrologists, taking for granted a positive ICaB (particularly when vitamin D metabolites and/or calcium-containing phosphate binders are used), hold that only a negative DCaB can counterbalance the trend toward a continuous overload of calcium with its oversuppression of PTH and bone turnover and possibly, a negative effects on vascular beds. A third group of nephrologists consider a null DCaB as the ideal one, as it is the only one able to avoid the negative consequences of either a positive or negative DCaB.

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*Seminars in Dialysis*—Vol 27, No 1 (January–February) 2014 pp. 4–7
DOI: 10.1111/sdi.12150

However, in addition to the practical difficulties in achieving a desired DCaB which will be addressed in the next section, there are at least two main considerations, which are worth discussing. The first is that we have no clear demonstration (or even an unclear one) that a negative DCaB might really counterbalance a positive ICaB (or the reverse situation). In fact, the movement of calcium into the various body calcium compartments probably differs substantially, depending on calcium's mode of entry into the body (from the intestine or by intravenous route). The possibility that an enteral calcium load exacerbates vascular calcification while a negative DCaB worsens CKD-MBD is not farfetched.

The second consideration arises from recent observations, which strongly suggest that the DCaB is not necessarily paralleled by concordant changes in ionized calcium concentrations after dialysis. In fact, a recent study reported that, while DCaB was positive with three different (1.25, 1.36, 1.50 mmol/l) dialysate Ca concentrations (although to different extents), the 1.25 mmol/l dialysate calcium reduced plasma ionized calcium (iCa) concentration with a concomitant increase in PTH. This was at variance with the other two dialysis concentrations, which were both followed by increased calcium and reduced PTH levels. These results not only confirm that the changes in serum calcium are an unreliable index of the DCaB, but also call attention to the need for taking DCaB and serum calcium changes into account separately when choosing a dialysate calcium concentration.

From a clinical point of view, these observations might not be trivial as the changes in serum calcium during dialysis have been implicated in the pathogenesis of some relevant adverse effects. Increased calcium concentration may induce an increased blood pressure and pulse wave velocity, the latter having recently earned the dignity of being considered a reliable and early index of arterial wall status (6–8). On the other hand, a reduction in calcium after dialysis has been reported to induce hypotension and increase QT interval, with consequent arrhythmias and the possibility of sudden cardiac death (9,10). However, not all authors have been able to confirm a relevant role for altered calcium concentration in the pathogenesis of the hemodynamic events observed during dialysis treatment (11,12).

Whatever the real importance of these findings, it is clear that when making the choice of dialysate calcium concentration, one needs to consider its impact on calcium balance and the change in serum calcium levels, with the awareness that these two aims might not necessarily be achieved at the same time.

## How to Achieve these Goals

The concentration gradient between serum and dialysate calcium and the ultrafiltration volume are the main variables determining the calcium movement into and out of the intra-corporeal pools and hence, determinants of both DCaB and the changes in serum calcium concentrations during dialysis treatment (2).

Theoretically, it appears to be an easy task to achieve the desired goals for DCaB and changes in serum calcium concentration (whatever they may be). In fact, once the serum calcium concentration of the patient and the operative modalities (namely, the diffusive and convective transports) of the specific dialysis techniques are known and established, the choice of an appropriate d-Ca could predict the resulting DCaB and/or serum calcium changes. However, in the real world, things are much more complicated than this. For one thing, it is actually the diffusible serum calcium (approximated by its ionized level) not the total concentration that is relevant to the diffusion gradient. As iCa is not routinely measured, a critical element of DCaB can only be estimated.

The studies addressing the topic of which d-Ca should be used to obtain a desired DCaB and/or change in serum calcium concentration have given contradictory results. There is substantial agreement that a d-Ca >1.50 mmol/l results in a positive DCaB and an increased serum calcium concentration, while a d-Ca <1.25 mmol/l has the opposite effect. However, in the gray zone in-between 1.25 and 1.50 mmol/l, negative, positive and null DCaB have all been reported, with variable changes in serum calcium concentration, sometimes not consistent with the DCaB (2,13–17). Furthermore, in individual patients, even these somewhat vague guidelines may be misleading—the hypercalcemic patient (especially, one requiring a high volume of ultrafiltration) may have a negative DCaB using a d-Ca above 1.50 mmol/l, while the hypocalcemic patient using a d-Ca less than 1.25 mmol/l may have a positive DCaB, particularly if little ultrafiltration is needed.

A number of potential factors might partially explain some of these discrepancies.

First, the available d-Ca concentrations are relatively inflexible with steps of 0.25 mmol/l between them: this is a huge amount considering that changes in serum calcium of <0.20 mmol/l may maximally stimulate or inhibit Ca-mediated PTH secretion (18). Furthermore, serum calcium concentrations can vary greatly among different patients and in the same patient over time, leading to highly different blood–dialysate gradients.

Second, serum calcium concentration changes during dialysis treatment, due to changes in the many factors which directly or indirectly affect calcium distribution in the different intracorporeal pools, such as hormonal (PTH), electrolyte (pH, phosphorus), cytokine, protein level changes, and extracellular volume variation, just to name the most relevant ones.

Finally, it is worth remembering that, although serum and dialysis concentrations of calcium are the

main driving factors, other variables can also play a role in determining calcium transport across the dialysis membrane, such as phosphorus and hydrogen ion concentration. Thus, the choice of one d-Ca concentration might not serve to obtain the desired DCaB and/or variation in s-Ca in all patients and in each patient over time.

An effective individualization of d-Ca should ideally be performed by an automatic system able to read in real-time the serum calcium level and adjust the d-Ca concentration to maintain the desired dialysis-to-serum calcium gradient throughout the treatment. Such a more finely tuned d-Ca producing system would probably more closely fulfill the expectations of those seeking an optimal individualization of d-Ca.

## Is It Worth Doing the Individualization of d-Ca

The final and very critical question is the real advantages of individualizing d-Ca in clinical practice. Again, separate discussions of the value of achieving a desired DCaB or a given serum calcium alteration are worthwhile.

Many nephrologists propose the choice of a negative or positive DCaB to compensate for a positive or negative ICaB, respectively. However, as previously outlined, it is mere speculation that this approach works. After all, the distribution and fate of calcium entering (and leaving) via two quite different routes (intravenous vs. intestinal) and over two substantially different durations of times (few hours vs. days) are physiologically quite dissimilar. Nevertheless, in the case of an obligate high intestinal calcium intake and/or active vitamin D utilization, or when the vascular calcification burden in a single patient is evidently high, it might be inadvisable to have a positive DCaB. On the other hand, in the case of a demonstrated low bone turnover condition, with reduced PTH levels, it might be worth seeking a negative DCaB, at least over a definite and limited period of time. However, in any of these conditions, the optimization of the medical treatment which determined the calcium status should be considered at the same time.

For the second issue, regarding the individualization directed to achieve a desired level of serum calcium, it should be borne in mind that rapid changes of serum calcium greatly affect PTH secretion and can have acute effects (indirect or direct) on vascular and heart activity. Furthermore, it is also worth considering that the hemodynamic effects are highly dependent on the gradient between serum calcium and d-Ca concentrations. In fact, a recent study showed (10) that a lower d-Ca used in the setting of a higher serum calcium increased the risk for sudden cardiac death; there was a nearly 50% increase in risk for each 1 mEq/l increase in the serum-to-dialysate calcium gradient.

This point deserves a particular comment in light of the newer drugs used for the control of secondary hyperparathyroidism in dialysis patients. As the use of active vitamin D metabolites and calcimimetics are often associated with increased and reduced serum calcium levels, respectively, many nephrologists think that it is wise to counteract these changes in calcium concentration using a low or a high d-Ca for correcting hypercalcemia and hypocalcemia, respectively; this clinical practice should probably be reconsidered. Indeed, in the former case, a greater acute reduction in Ca concentration is expected when extremely low d-Ca is used and this might induce a brisk stimulation of PTH secretion, hemodynamic instability and possibly negative cardiac effects. On the other hand, when a high d-Ca is used for counteracting the hypocalcemic effect of cinacalcet, an excessively positive calcium balance is expected due to the increased dialysis-to-serum calcium gradient; this might further reduce bone turnover and potentially increase vascular calcification. In fact, when hypercalcemia is present due to an over-dosage of hypercalcemic drugs (vitamin D metabolites, Ca-containing phosphate binders), it would be more advisable to taper or stop these drugs and avoid very low d-Ca concentrations to both limit the stimulatory effects on PTH and prevent adverse cardio-vascular effects. When cinacalcet-dependent hypocalcemia needs to be corrected, it is much more advisable to reduce or stop the drug and/or to increase vitamin D, and not use a high d-Ca so that an excessively positive DCaB can be avoided.

As there is no effective automatic system yet to achieve a real individualization of d-Ca, use of the rough individualized approach recently described by Jean and coworkers might be considered (19). Using this approach, d-Ca concentrations are adjusted from 1.25 to 1.50 or from 1.50 to 1.75 mmol/l or vice versa according to the levels of PTH and serum calcium. The authors demonstrated better control of PTH and calcium levels both in patients requiring a reduction in PTH and in those needing an increase. In addition to the potential limitations of such an approach mentioned in the previous paragraphs, the proposed method was not an easy task; it was time consuming and required many complicated organizational steps. So, in order to evaluate the real cost-effectiveness of this strategy, a controlled trial would be required.

## Concluding Remarks

Although individualizing d-Ca might theoretically lead to a useful improvement in dialysis treatment, many aspects remain to be elucidated before concluding that it offers definite clinical advantages. We still do not know what the exact goals of such an individualization should be nor do we, as yet, have a reliable means of achieving them. Finally, we have no clear demonstration that any proposed approach is safe and cost-effective. Again, whilst waiting for a device which can fine-tune d-Ca in real-time against serum calcium level, it is our opin-

ion that one should seek a neutral Ca balance by using a d-Ca concentration as close as possible to a patient's serum iCa concentration with an upward adjustment of about 0.25 mmol/l (for typical levels of convective Ca loss to the dialysate) (20) to avoid unpredictable effects on mineral metabolism and, possibly, on the cardiovascular system as well.

## Acknowledgments

The Writing of this paper has been supported by the grant 'Project Glomerulonephritis' in memory of Pippo Neglia.

## Conflict of Interest

No conflict of interest relevant to this paper is declared.

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