Dialysate calcium concentration during calcimimetic treatment: a neglected issue

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Hypocalcaemia is a well-known effect of the treatment of secondary hyperparathyroidism when using calcimimetics.

In a retrospective, observational, study, which was published recently in this Journal [1], Louie et al. investigated the frequency, predictors, and consequences of cinacalcet-induced hypocalcaemia in a cohort of over one thousand haemodialysis patients. They found that hypocalcaemia occurred in more than two third of the treated patients and was mild in many cases. Nonetheless, in one third it was moderate ($1.87 < 2.0$ mmol/L; 23%) or even severe (< 1.87 mmol/L; 9%). These results coming from a “real-world” setting raise questions on the true potentially negative impact of hypocalcaemia per se or of its treatment, including the increase of dialysate calcium concentration.

In this study, intact parathyroid hormone (iPTH) did not increase following hypocalcaemia and, most importantly, the rates of death and cardiovascular events were comparable between hypocalcaemic and non-hypocalcaemic patients. Moreover, non-significant changes occurred in the dialysis schedule and in drug prescriptions over the study. However, a dialysate calcium concentration > 1.5 mmol/L was used in a significant percentage of patients. In the presence of hypocalcaemia, this is expected to increase significantly the intradialytic calcium mass balance, at standard ultrafiltration rate, with possibly unfavourable clinical effects in the long term. Considering that the cardiovascular follow up was limited to 12 months, this question cannot be answered by the data of this study.

Correcting hypocalcaemia by increasing dialysate calcium means giving the patient a large amount of calcium in a few hours and in the wrong moment (i.e., simultaneously with the correction of metabolic acidosis!).

The management of electrolyte balance is critical in chronic kidney disease (CKD), sometimes requiring emergency intervention in life-threatening situations. In patients with CKD stage-5 dialysis (CKD-5D), the management of electrolyte balance is even more complicate, since haemodialysis is usually performed three times a week for 4 h with a great impact, among the rest, on the body fluid compartments, electrolyte mass balance and concentrations. In this respect, the role of the dialysate composition is of key importance, in particular for calcium. Indeed, CKD 5D patients are at high risk of cardiovascular and parenchymal calcifications, which heavily affect long-term outcome; the regulation of calcium metabolism is hence critical. In this context, the choice of an adequate dialysate calcium concentration (d[Ca]) is an important aspect. Despite this, the topic has been hotly debated, and many grey areas still need clarifications. To confirm this, most of the recommendations of recent guidelines are mainly based on experts’ opinions, with only a few based on evidence [2]; and the adequate d[Ca] in relation to the patient ionized plasma water calcium concentration is among the debated issues [3, 4], particularly when using calcimimetics for the treatment of secondary hyperparathyroidism (SHPT).

Today, calcimimetics, such as cinacalcet and etelcalcetide, represent the treatment of choice of SHPT in many patients. Differing from vitamin D sterols, they do not increase serum levels of calcium phosphate and fibroblast growth factor 23 (FGF23) (a hormone associated with cardiovascular mortality in dialysis patients [5]). Nonetheless, they produce hypocalcaemia, which inevitably affects intradialytic calcium balance.

There is general agreement that an adequate d[Ca] is needed to prevent or at least reduce the clinical complications of severe SHPT, including cardiovascular, parenchymal

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and soft tissue calcifications. However, there are two opposite approaches to the same purpose, underlying the lack of a consensus among experts.

Some authors support the use of low $d[Ca]$ to reduce the long-term risk of cardiovascular and valvular calcification [6, 7]; others suggest to avoid low $d[Ca]$, because of the risk of worsening SHPT [8] and of favouring dialysis hypotension and cardiac arrhythmias.

Clinically, there is consensus that intra-dialytic calcium balance should be tailored to patient needs, but unfortunately there is still no reliable method to quantify the intra-dialytic calcium mass balance. We know that during haemodialysis, calcium fluxes are driven by two usually opposite mechanisms: convection and diffusion. Incorrectly, nephrologists might consider an increase of total plasma calcium concentration during haemodialysis as an index of positive calcium balance. However, this does not take into account the amount of calcium removed by convection. Indeed, if the amount of calcium removed by convection is higher than the amount gained with diffusion, as in the case of high ultrafiltration volumes, the calcium balance will be negative, even in the face of increased plasma calcium concentration secondary to gradient-dependent diffusion from the dialysate. Further complicating the picture (Fig. 1), during haemodialysis the total calcium concentration increases along with the increment in total protein and the eventual Donnan's effect resulting from ultrafiltration rate. Thus, more than total calcium, as a more appropriate measuring method, the ionized plasma calcium concentration should be better used and corrected for the dialysis dependent changes of blood pH, since alkalosis occurring during haemodialysis reduces the solubility of ionized calcium [9]. For this reason, even the methods based on ionized calcium may overestimate calcium metabolism if the pH-related variation in ionized calcium concentration is not taken into account [10]. Also, bone turnover is an

additional variable that can affect calcium mass balance during haemodialysis, and patients with high bone turnover are predicted to handle calcium fluxes better than those with low turnover disease. Finally, it is also worth noting that the true calcium concentration of dialysate bags is often lower than the “nominal” one reported in the label [10].

In an effort to find a simplified method of estimation, Di Filippo et al. [10] evaluated the intradialytic calcium mass balance by applying the Single-Pool Variable-Volume Calcium Kinetic Model (SPVV-CaKM) suggested by Gotch et al. [11]. In particular, they investigated on real clinical data obtained by implementing the model in dialysis patients, the SPVV-CaKM accuracy in predicting the serum calcium concentration at the end of the dialysis session by using a different set of parameters (Donnan's factor and calcium effective ionic dialysance) in respect to the model suggested by Gotch et al. [11]. Using a nominal $d[Ca]$ of 1.50 mmol/L, most of the patients showed a negligible difference between measured and predicted end-dialysis plasma water ionized calcium concentration. This suggests that the model was accurate and allowed an estimation of the dialysis calcium mass balance to be possibly used for individualized $d[Ca]$ prescription. Interestingly, by using this fixed nominal dialysate calcium concentration, calcium mass balance varied widely not only between patients but even in the single patient according to its pharmacological treatment (cinacalcet in this case) [10].

Altogether, the issue of $d[Ca]$ during calcimimetic treatment is a key aspect not to be overlooked.

In the paper by Louie et al. [1], in comparison with those who were normocalcaemic, the patients with severe hypocalcaemia were more often diabetic, overweight, had cardiovascular disease, a shorter dialysis vintage, used a central vein catheter as dialysis access, were prescribed fewer active vitamin D sterols, and had higher C-reactive protein (CRP)

Fig. 1 Calcium balance during dialysis is influenced by several factors: diffusion from dialysate to blood; convection from blood to dialysate; changes in pH from acidosis to alkalosis; increments in albumin concentration during dialysis and bone turnover. Since albumin is negatively charged, its increment results in a reduced amount of exchangeable calcium secondary to changes in ionized calcium concentration and to the Donnan's effect due to the total protein concentration. High or low bone turnover will offer a completely different avidity and handling capacity of the calcium fluxes

and iPTH and lower baseline calcium levels. Notably, even in severe cases, hypocalcaemia was mostly asymptomatic, transient with or without targeted intervention to correct it and was not associated with increased cardiovascular events or deaths.

At multivariate analysis, central vein catheter as vascular access, low albumin and high iPTH were among the predictors of hypocalcaemia [1]. As reported nearly two decades ago by Polaschegg et al. [12], if the double-lumen of a central venous catheter is filled with citrate locking solutions, up to 15% of the solution is spilled into the blood of the patient, causing a decrease of plasma water ionized calcium concentration.

Interestingly, in the discussion the authors report that short-term adjustments of d[Ca] might not have been captured in severely hypocalcaemic patients and that, in any case, they had no clear evidence for any systematic trend towards higher d[Ca] in those with hypocalcaemia [1]. However, we would have possibly expected a decrease and not an increase in d[Ca]. In fact, we strongly believe that an excessive gradient between the d[Ca] and the patient ionized plasma water calcium concentration should be absolutely avoided, in order to prevent an excessive calcium flux into the blood and then into the organs in a very short period of time (usually 4 h), while the patient is likely having a switch from a state of metabolic acidosis to one of metabolic alkalosis, further favouring the precipitation of calcium salts in the cardiovascular system and parenchyma. This could be especially undesirable if the patient responds to treatment with a significant drop in iPTH levels and bone turnover. In case of need, the correction of severe asymptomatic hypocalcaemia should be carefully accomplished during the interdialytic period, by giving to the patients refracted doses of calcium supplements and sufficient doses of vitamin D.

In conclusion, at present there is no consensus on the best management of calcium mass balance in CKD-5D patients, mostly because the pathogenesis and progression of mineral-related disorders (e.g., coronary calcifications and calcific uremic arteriopathy) are not completely understood. Instead, there is agreement that an adequate d[Ca] is of paramount importance in preventing or at least reducing renal bone disease, cardiovascular and parenchyma calcifications, together with intradialytic arrhythmias and hypotension. In this respect, the handling of the intradialytic calcium mass balance (and plasma water ionized calcium concentration) to achieve these goals is a crucial aspect, possibly influenced also by the use of calcimimetics [10]. In our opinion, it is very important to avoid an excessive gradient between the d[Ca] and the plasma water ionized calcium concentration, in order to prevent an excessive amount of calcium from reaching the blood and then the organs of the patients in the very short period of the dialysis session. As outlined, the total calcium mass balance depends not only on d[Ca], but

also on pre-dialysis plasma water ionized calcium concentration, total ultrafiltration, correction of metabolic acidosis and bone turnover. Therefore, it is unlikely that one dialysate calcium concentrations may fit all. This seems particularly true considering the great variability of patients' drug prescriptions for serum iPTH, calcium and phosphate control. An integrated (but still empirical) approach encompassing all these factors is needed for a personalized d[Ca] prescription that takes into account the complexity of water and electrolyte fluxes during haemodialysis and which would predictably improve the management of calcium metabolism in CKD-5D patients. In the meanwhile, the results of the present study [1] is further reassuring on the safety of even severe asymptomatic hypocalcaemia associated with calcimimetic therapy.

Compliance with ethical standards

Conflict of interest FL is or was a member of an advisory board or speaker at meeting supported by Amgen, Baxter, B.Braun and Vifor Pharma. SM was speaker at meetings supported by Amgen and Vifor Pharma; SR and LDV have no conflict of interest to declare in respect to the present paper.

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