How do we have to use the calcium in the dialysate to optimize the management of secondary hyperparathyroidism?

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Introduction

Hyperparathyroidism, adynamic bone disease, osteomalacia and β2-microglobulin amyloidosis are all conditions involving bone that may be observed in chronic renal failure patients. Their relative incidence varies amongst different series, and is certainly influenced by the progress achieved in their respective diagnostic and treatment. β2-Microglobulin amyloidosis, which was clinically described and biochemically characterized in the 1980s [1,2], was missing in the early reports on renal bone disease. Adynamic bone disease, which seems to be less innocuous than thought earlier, is increasing in frequency [3]. Hyperparathyroidism is still the most frequent cause of clinically expressed renal bone disease, despite the improvement achieved in its treatment and prevention.

The parameters influencing the secretion of parathyroid hormone (PTH) are calcium, phosphate and vitamin D₃. The homeostasis of these parameters is strongly interrelated in normal subjects, and the metabolism of each of them may be disregulated in renal failure. Hyperphosphataemia was one of the first factors to be identified as an inducer of hyperparathyroidism [4], and very recently its direct effect on PTH secretion has been proven [5]. Vitamin D deficiencies are known to participate in hyperparathyroidism; vitamin D₃ has a depressive effect on PTH synthesis [6] and supplementation with active vitamin D₃ derivatives is an effective treatment even of severe forms of hyperparathyroidism [7]. It is, however, important to stress that the most powerful stimulus of PTH secretion is hypocalcaemia, as this may result in >2-fold the increase induced by hyperphosphataemia [8]. Therefore, Ca balance and regulation are very important when treating hyperparathyroidism.

The history

Dialysate Ca concentration (dCa) was one of the first parameters which renal physicians studied to deal with hyperparathyroidism. Fournier et al. observed that the use of a dialysate Ca concentration <5.7 mg/dl (1.42 mM) was the major risk factor in developing bone disease [9], and Johnson proposed to increase the dCa to 1.75 mM in order to prevent hyperparathyroidism [10]. This approach was unchallenged for more than two decades, until aluminium-containing salts lost favour as phosphate binders because of their proven toxicity. The introduction of Ca-containing phosphate binders in clinical practice was found to be limited by hypercalcaemic episodes, and lowering the dialysate Ca concentration to 1.25 mM was proposed, with promising results in handling Ca–phosphate metabolism in dialysis patients [11].

Our experience with 1.25 mM dialysate Ca and present approach

We adopted a 1.25 mM dialysate Ca concentration and prospectively studied the effects on Ca transfers acutely during the dialysis session and in the long term on hyperparathyroidism. We observed a significant increase in intact serum PTH in the group of patients treated with 1.25 mM dialysate Ca concentration when compared with a control group treated with 1.5 mM [12] (Figure 1). Equivalent results were subsequently reported by Fernández et al. [13]. After these observations, we changed our standard dialysate Ca concentration to 1.5 mM, and currently we reserve 1.25 mM dCa for selected cases with hypercalcaemia and patients compliant for the CaCO₃ treatment (our approach has been discussed in detail in [14]).

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Optimization of calcium dialysate concentration

Observations of calcium dialysate concentration observed in the 'hard water syndrome'; hypertension, cephalgia, nausea, vomiting, and various neurological disorders. However, the Ca concentrations used in dialysis clinics (<1.75 mM) do not induce any of these symptoms, unless there is a dysfunction in the water treatment and a real hard water syndrome, producing dCa > 1.75 mM.

In the long term, where does the Ca given to the patient go? Are we favouring metastatic soft tissue calcifications? First of all, it is difficult to evaluate how positive the Ca balance is; it is impossible to calculate it by measuring the blood side, unless one is using labelled dialysate Ca. The study of total balances in haemodialysis techniques is far easier when monitoring dialysate. Spent dialysate monitoring may be performed readily by simply adding an automatic syringe which will continuously pull a constant volume from the dialysate outlet [20]. We think that simple devices allowing a precise quantification of balances of any dialysable substance should be used more frequently in clinical practice [20]. Our studies using spent dialysate showed that patients with serum Ca in the normal range before dialysis have a clearly negative balance when treated with 1.25 mM and a nil balance when treated with 1.5 mM dialysate Ca concentration [18].

Secondly, for those situations with a clear positive Ca balance, the increase in serum Ca may enhance soft tissue calcification; however, the possibility also exists that an important part of the Ca given to the patient goes to her/his bone; something that would be, to our view, beneficial to the patient, and that probably depends on bone metabolism (adynamic bone disease being less likely to incorporate Ca). Serum Ca is not the only factor influencing soft tissue calcification; there is no evidence showing that serum Ca is the most important factor. The Ca-phosphate product, magnesium, alkalosis and other local factors may participate [10]. Since the variations in absolute values in serum phosphate are usually greater than those of Ca, phosphate could well be even more important than Ca. We have observed very fast growing ab-articular calcifica-

The doubt: is it dangerous to use > 1.5 mM dCa?

Our experience convinced us that it is harmful to use 1.25 mM dCa indiscriminately. Is it harmful to use > 1.5 mM dCa indiscriminately? The putative acute risks of positive Ca balances during dialysis are those observed in the 'hard water syndrome'; hypertension, cephalgia, nausea, vomiting and various neurological disorders. However, the Ca concentrations used in dialysis clinics (<1.75 mM) do not induce any of these symptoms, unless there is a dysfunction in the water treatment and a real hard water syndrome, producing dCa > 1.75 mM.

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tions in a patient during the post-parathyroidectomy period, with low to normal Ca and very high serum phosphate (un-reported observation). As commented by Hsu in his recent review [21], visceral calcifications were frequent in dialysis patients [22], but they were also frequently observed in non-dialysed renal failure patients, in whom it is difficult to imagine a positive Ca balance and hypercalcaemia [22].

Finally, cardiac valve calcifications, a disconcerting clinical finding, are classically associated with severe hyperparathyroidism. Thus, severe hyperparathyroidism may be more detrimental for the patient than a positive Ca balance without hyperparathyroidism.

Conclusion

Handling the metabolic complications of end-stage renal failure patients is a very difficult exercise, as many of the disregulated factors are interrelated. Ca metabolism and renal bone disease represent an illustrative example of these interrelationships. In our and others’ experience, using low dialysate Ca concentration (1.25 mM) has been shown to worsen secondary hyperparathyroidism [12,13]. Our Ca mass balance studies showed that for a patient with normal serum Ca before dialysis, 1.25, 1.5 and 1.75 mM dialysate Ca concentrations result respectively in a clear negative, nil and a clear positive Ca balance for the patient. Consequently, we have chosen 1.5 mM as the first-choice dialysate Ca concentration. However, the dialysate Ca concentration must be individualized; 1.75 mM may be used temporarily for Ca-depleted patients, and 1.25 mM dialysate Ca concentration may be used for those patients with a tendency to hypercalcemia and good compliance with their CaCO₃ treatment, also on a temporary basis. Our clinical practice is very much in agreement with the recommendations recently made by Felsenfeld in his review: “if a 2.5 mEq/l (1.25 mM) dialysate calcium is used, the nephrologist managing the patient must be vigilant to note increases in PTH levels and change the dialysate Ca concentration accordingly” [23]. A given dialysate Ca concentration has to be prescribed based on Ca mass balance studies and should be adapted for each patient at the precise moment, according to the benefits for his/her renal bone disease, by loading or depleting Ca during dialysis.

References