Biological impact of targeted dialysate calcium changes in haemodialysis patients: the key role of parathyroid hormone

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Abstract
Background. Establishing an optimal dialysate calcium (DCa) concentration in haemodialysis patients is crucial. DCa individualization has been advocated but most dialysis centres use a fixed DCa, preferably 1.25 mmol/L in the USA and 1.5 mmol/L in European countries. The aim of the study was to assess the short-term biological impact of individual DCa prescription aiming at maintaining normal serum calcium and serum parathyroid hormone (PTH) between 150 and 300 pg/mL.

Methods. Between January 2008 and December 2010, all prevalent patients were checked for the need for DCa change according to our usual strategy. Baseline (T0) and after 3 months (T3), values were compared for serum calcium, phosphate, total alkaline phosphatases (t-ALP) and PTH.

Results. Seventy-eight patients were followed up for analysis with only one DCa change. Vitamin D derivatives, oral calcium and cinacalcet doses remained stable. Increasing DCa from 1.25 to 1.5 mmol/L and from 1.5 to 1.75 mmol/L led to a significant increase of calcaemia (+2.2 and +1.7%) and a decrease of phosphataemia (−7 and −9%), t-ALP (−10 and −12%) and PTH (−50 and −62%). Decreasing DCa from 1.75 to 1.5 mmol/L and from 1.5 to 1.25 mmol/L led to a decrease of calcaemia (−2.5 and −1.7%) and an increase of phosphataemia (+11 and +12%), t-ALP (+12 and +10%) and PTH (+138 and +175%).

Conclusions. DCa individualization has a significant impact on mineral metabolism parameters, especially on serum PTH levels, and could be considered as an additional therapy in a more global strategy together with phosphate binder, vitamin D and calcimimetics prescription.

Keywords: alkaline phosphatases; dialysate calcium; haemodialysis; parathyroid hormone; phosphorus

Introduction

The optimal dialysate calcium (DCa) concentration in haemodialysis (HD) patients remains highly controversial [1, 2]. The amount of calcium exchange during HD depends on DCa concentration but also on the patient’s ionized calcium, the ultrafiltration rate and probably the bone turnover [3]. Manipulation of DCa leads to a change in the calcium balance and impacts on serum calcium, phosphate and parathyroid hormone (PTH) levels, bone disorders and possibly cardiovascular disease [4]. DCa prescription should be taken into account together with oral calcium, calcimimetics and vitamin D derivates. Besides, DCa also impacts on the haemodynamic stability during dialysis session [5].

In 2003, the Kidney Disease Outcomes Quality Initiative (KDOQI) recommended a standard DCa concentration of 1.25 mmol/L with a poor level of evidence and mainly based on the US habit using large intravenous calcitriol administration and calcium-based phosphate binders [6]. However, the KDOQI experts stated that DCa should be individualized according to serum PTH and calcium levels using higher DCa in cases of hypocalcaemia and high bone turnover and using lower DCa in cases of hypercalcemia and low bone turnover, but this individualization appears time consuming.

In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggested using a DCa between 1.25 and 1.5 mmol/L in HD patients and that the DCa therefore should be adjusted to optimize the total body calcium load [7]. Theoretically, this strategy should help to improve bone health by reducing calcium flux during dialysis in patients with adynamic bone disease (ABD) and extraskeletal calcification and by inducing positive calcium flux during dialysis in patients with hypocalcaemia. They concluded that it is probably wise to maintain flexibility with dialysate calcium concentrations, which should be individualized, whenever possible, to meet specific patient requirements.

The aim of the present study was to assess the short-term biological impact of an individual DCa prescription aiming at maintaining normal serum calcium and serum PTH between 150 and 300 pg/mL.

Materials and methods

Between January 2008 and December 2010, all prevalent patients were checked for the need for DCa change according to our usual strategy.

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This strategy was to decrease the DCa in cases where serum PTH is <150 pg/mL without hypocalcaemia or in cases of hypercalcaemia (≥2.5 mmol/L) and to increase the DCa in cases where serum PTH is >300 pg/mL without hypercalcaemia or in cases of hypocalcaemia. Two successive measures were performed to confirm the values at 1-month intervals. Available DCa concentrations were 1.25, 1.5 and 1.75 mmol/L.

HD sessions were performed using a 3 × 4 to 3 × 8 h schedule, high-flux polysulphone membrane and online haemodiafiltration for most of the standard 3 × 4 h schedule.

Serum PTH levels (Elecsys; Roche Diagnostics, Meylan, France; reference value 10–65 pg/mL) and total alkaline phosphatase levels (t-ALP Roche colorimetric; normal value <270 U/L for men and <240 U/L for women) were assessed every month with usual biological parameters.

We performed a retrospective analysis using some exclusion criteria: chronic liver disease, proven by liver biopsy, accompanied by elevated serum gamma glutamyl transferase levels; significant changes in therapy and dialysis prescription during the observational period; dialysis session time >6 h and observational period of <6 months.

Only stable patients having only one DCa change were recorded. Baseline parameters (T0) were recorded using the mean of the two last values for serum PTH, t-ALP, calcium and phosphorus before the DCa change. These initial values were compared to the mean of the two monthly values obtained 3 months after the DCa change (T3). According to the DCa changes, patients were put into four groups: 1.25–1.5, 1.5–1.75, 1.75–1.5 and 1.5–1.25 mmol/L.

### Statistical analysis

Initial and final values for serum PTH, t-ALP, total calcium and phosphorus were compared using paired t-test and the difference was expressed as percentage. Results are reported as mean ± SDs. Differences with P-values ≤0.05 were considered statistically significant. Statistical analyses were performed using MedCalc© software, version 9.3.1.0, Belgium.

### Results

Between January 2008 and December 2010, 345 prevalent HD patients were checked for inclusion. Two hundred and eighty-five patients had at least one DCa change: 155 patients had only one, 95 had two, 30 had three and 5 had more than three changes. Seventy-seven out of 155 were excluded due to dialysis treatment sessions being longer than 6 hours, a comorbidity with liver disease (n = 12), an observational period of over 6 months (n = 7), or significant changes in treatment (n = 27). Thus, seventy-eight patients were followed up for analysis with only one change.

Changing DCa was applied as a first-line therapy in cases where compliance with the oral treatment was poor, when phosphate levels were not controlled despite an aggressive phosphate-binder therapy preventing increasing calcitriol analogues in cases of high PTH levels or when willing at maintaining current therapy.

The baseline characteristics of the four groups are shown in Table 1. Patients needing a decreased DCa had lower serum PTH (68.1 ± 26 and 112 ± 45 pg/mL) than patients needing an increased DCa (345 ± 48 and 481 ± 131 pg/mL). They also have lower t-ALP (173 ± 47 and 169 ± 32 U/L versus 254 ± 63 and 274 ± 119 U/L) leading to the biological diagnosis of ABD. Caemia and phosphataemia were not statistically different. All patients were treated with cholecalciferol, no patient had history of parathyroidectomy (PTX).

The evolution of the four parameters between the two periods is shown in Figures 1–4. Increasing DCa never led to hypercalcaemia and allowed decreasing serum PTH sometimes dramatically. On the other hand, decreasing DCa never led to hypocalcaemia but allowed increasing serum PTH >150 pg/mL in most cases.

Decreasing DCa led to a significant decrease in calcaemia (−1.7 and −2.5%) and an increase in...
phosphataemia (+11 to +12%) and t-ALP (+11 and +12%) but mostly in serum PTH (+138 and +175%).

Increasing DCa led to a significant increase in calcemia (+1.7 and +2.2%) and a decrease in phosphataemia (−7 and −9%), t-ALP (−10 and −12%) and mostly in serum PTH (−50 and −62%).

**Discussion**

Using an individualization of DCa by increasing or decreasing its concentration by 0.25 mmol/L according to serum calcium, PTH and t-ALP concentration, we report here a homogeneous short-term biological impact.
DCA in the HD patient could be adjusted to manage the calcium balance and indirectly the bone turnover by the PTH-related changes. It is postulated that the optimization of the bone metabolism may also improve the cardiovascular calcification and the related mortality. The appropriate DCA could be individualized depending on few variables. We chose to prescribe DCA based on serum level of total calcium, PTH and t-ALP as a part of our homogeneous strategy previously reported [8].

In the early 1960s, DCA was set at 1.25 mmol/L in order to fit the ionized calcium, but higher DCA was required to prevent hypocalcaemia and high bone turnover disease [9]. Hyperphosphataemia, vitamin D deficiency, diminished hydroxylation of 25 OH vitamin D and restricted dietary calcium intake may explain the frequent hypocalcaemia and secondary hyperparathyroidism (SHPT). In the 1980s, the administration of calcitriol or analogues, together with the widespread use of calcium-based phosphate binders, led to the decrease of DCA in order to

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**Fig. 3.** Evolution of predialysis serum PTH levels after DCA changes. Mean ± SD. *P < 0.05; **P < 0.005; ***P < 0.0005 between the two periods.

**Fig. 4.** Evolution of predialysis serum t-ALP level after DCA changes. Mean ± SD. *P < 0.05; **P < 0.005; ***P < 0.0005 between the two periods.
prevent excessive calcium load, ABD and hypercalcaemia [10]. The more recent use of non-calcium phosphate binders and calcimimetics has made more crucial the optimization of the DCa. The association of non-calcium phosphate binder may lead to a negative calcium load with the potential of PTH stimulation; this can be exacerbated by a low DCa prescription.

In 2003, the KDOQI recommended to set the DCa at 1.25 mmol/L in cases using calcium salt and/or calcitriol analogues [6]. The need for individualization was recognized but not recommended for practical reasons. In European countries, a standard DCa of 1.5 mmol/mL has been advocated in patients taking calcium salts and vitamin D derivatives and 1.75 mmol/L in others cases. A DCa of 1.25 mmol/L should be avoided for prolonged use due to the risk of SHPT [11]. In 2005, the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported a mean DCa of 1.45 mmol/L worldwide with great variation between countries and centres but remained lower in the USA as compared with European countries and Japan [12]. The last KDIGO recommendations stated that DCa should be set between 1.25 and 1.5 mmol/L and could be individualized to meet specific patients’ requirements [7].

In 2010, Gotch et al. hypothesized, based on a calcium kinetics model, that only a DCa dose of 1.25 mmol/L was warranted to achieve a positive calcium balance in most HD patients [2]. However, this model has been challenged by Moe and Druke [1].

The diffusion of Ca in HD depends greatly on the gradient between DCa and serum diffusing calcium concentration. Most studies reported that, when DCa is >1.5 mmol/L, there is a positive calcium balance during the session [13]. A DCa of 1.25 mmol/L provides a neutral or negative Ca balance [14]. The Ca loss due to convection should be taken into account especially when using haemodialfiltration.

High DCa has been associated with greater haemodynamic stability [15]. A 1.25 mmol/L DC has been associated with 90Tc dispersion and the risk for arrhythmia [16]. The cardiac effect of low DCa has not been assessed in our study even if one patient reported more dialysis discomfort when decreasing DCa to 1.25 mmol/L.

Far from mathematical models, our strategy was to provide the optimal amount of calcium, in each case, required to meet the patient’s needs. We do not believe that achieving a ‘neutral calcium balance’ would help to treat mineral metabolism disorders since most patients have previously experienced either a positive calcium balance, with low serum PTH and high calcium levels, or a negative calcium balance with low serum calcium levels and SHPT.

In our study, increasing DCa led to slightly increased calcaemia and decreased phosphataemia, serum t-ALP and above all PTH levels. This effect is close to that reported using calcium carbonate as a phosphate binder [17]. Apart from the impact on calcaemia, this effect is also close to that observed after cinacalcet therapy for the variation of serum PTH and phosphorus [18]. The effect on calcaemia and PTH is close to that reported using calcitriol analogues [19]. We think that increasing DCa should be considered in all cases of SHPT without hypercalcaemia. Interestingly, this effect was not influenced by the session length. In 1976, Reagan et al. [4] reported that increasing DCa from 1.15 to 1.5 mmol/L and from 1.5 to 1.75 mmol/L in 20 HD patients results in an unpredictable biological impact but a tendency to decrease serum PTH and increase serum calcium and phosphorus. Increasing DCa from 1.25 to 1.5 mmol/L has been shown to be associated with a decreased serum intact PTH (~50%) without changes in Ca × P product in HD patient without hypercalcaemia and low bone turnover profile [20]. It is hypothesized that the effect of DCa on phosphataemia depends upon bone turnover evolution. Lowering bone turnover from severe SHPT may lead to a decrease in phosphate release from the bone. But decreasing bone turnover to ABD may lead to increase phosphataemia because the bone cannot buffer phosphates. Besides, increasing DCa may help in treating hypocalcaemia in cases where oral calcium and vitamin D are unable to normalize calcaemia.

In our study, decreasing DCa of 0.25 mmol/L led to a slight decrease in calcaemia and increased serum phosphate, t-ALP and above all PTH levels. The aim of this change was to increase bone turnover and serum PTH in cases where ABD was suspected. We have previously reported that decreasing DCa from 1.6 to 1.5 mmol/L may favour SHPT [21]. Malberti et al. [10] reported a significant increase in serum PTH and t-ALP 12 months after decreasing DCa from 1.75 to 1.5 mmol/L. In 1991, Hou et al. [22] reported a decrease in phosphataemia after decreasing the DCa from 1.75 to 1.25 and 0.75 mmol/L but the phosphorus mass transfer remained stable. Lowering DCa from 1.75 to 1.25 mmol/L has been shown to improve Ca × P product and bone turnover of HD patient with biological signs of ABD [23]. The discrepancy between the small changes in calcaemia and the huge serum PTH variations has been reported previously and is suspected to be related to the tight regulation of calcaemia by PTH [20]. Therefore, the pre-dialysis total calcium may not reflect the calcium balance. Moreover, using only total calcium levels may not allow the adequate assessment of the real variation in ionized calcium [24].

In 2001, Palmer et al. and later Lindley et al. advocated the individualization of DCa prescription [25, 26]. Druke et al. [27] advocated a DCa between 1.5 and 1.75 mmol/L in cases of high PTH level or cinacalcet treatment and of 1.25–1.5 mmol/L in case of low bone turnover in addition to calcitriol and oral calcium prescription.

In a global strategy, lowering DCa allows the prescription of calcium-based phosphate binders and active vitamin D with less risk for ABD. A standard DCa of 1.5 mmol/L appears an appropriate choice in 50% of the cases in our experience using calcium-based phosphate binder in 40% of cases and active vitamin D in 20% of cases. We have previously reported that the individualization of DCa using the same criteria may help achieve recommended biological targets more frequently [8].

In cases of daily nocturnal dialysis session, there is less need for phosphate binders, especially calcium-based, and this should be compensated by increasing DCa [28]. For this reason, we chose to exclude patients using long-dialysis sessions with less need for phosphate binders.

A 1.75 mmol/L DCa is effective in decreasing PTH and bone turnover but some are afraid of hypercalcaemia and
metastatic calcification related to the intradialytic calcium load. In the DOPPS study, higher DCa was associated with higher all-cause mortality but less risk for PTX [12]. However, it is not known if DCa has been prescribed on an individual basis or if, more probably, DCa has been set according to the local habit. In this case, higher DCa prescribed in case of ABD may lead to hypercalcemia and the risk for vascular calcification. Hence, London et al. [29] reported that the risk for vascular calcification related with calcium load is dependent on the bone turnover. Besides, a DCa of 1.37 mmol/L has been shown to be associated with progression of aortic stiffness in HD patients as compared with a DCa of 1.12 mmol/L [30]. We think that our strategy with individual DCa prescription using monthly t-ALP and PTH dosage and bimonthly calcium and phosphate sampling allows prevention of such hazardous evolution by excess calcium load. Besides, we have recently reported that calcium carbonate use is associated with better survival than sevelamer in an observational French HD cohort [31]. We hypothesized that prescribing calcium salt mainly in case of hypocalcaemia and in a real-life condition may explain this beneficial effect. As a matter of fact, calcaemia remained lower in patients receiving calcium salt as compared with patients receiving sevelamer. In our experience, using higher DCa was not associated with the prevalence of peripheral vascular calcification [32] nor with their progression [33]. So we think that the relationship between high DCa and the risk for vascular calcification and mortality is not still clearly determined.

We have previously observed a relationship between high serum fibroblast growth factor (FGF)-23 level and poor outcomes in dialysis patients [34]. The factors associated with high serum FGF-23 levels were high serum calcium, phosphate, PTH and calcitriol levels. The effect of varying the dose of DCa on serum FGF-23 levels has not yet been investigated. However, the effect could be evaluated and may represent another biological target for individualized therapy.

Limitations

Our study is observational using retrospective data in selected cases. Patients having concomitant treatment adjustment have been excluded as those needing further DCa adjustment. The level of serum PTH target used in our centre is debatable but the KDOQI targets were largely applied at the time of the study. The haemodynamic stability has not been studied during our study. We have not measured regularly the ionized calcium but only total calcium. Lastly, it is a small study sample.

Conclusions

An individual prescription of DCa using 1.25, 1.5 and 1.75 mmol/L based on calcaemia, serum PTH level and bone turnover markers can help improve bone mineral abnormalities. After 3 months, increasing DCa of 0.25 mmol/L leads to a significant decrease of serum PTH and t-ALP level and with a slight increase in calcaemia. Decreasing DCa had a similar inverse impact. Together with other medications, DCa individualization could be included in a large strategy in order to optimize mineral metabolism abnormalities.

However, further studies are required before making definitive recommendations, and the mid-term safety of higher DCa doses should be assessed using targeted individual prescriptions.

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(See related article by Messa. The ups and downs of dialysate calcium concentration in haemodialysis patients. Nephrol Dial Transplant 2013; 28:3–7.)

References

Biofeedback dialysis for hypotension and hypervolemia: a systematic review and meta-analysis

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Abstract

Background. Intradialytic hypotension (IDH) is associated with morbidity and mortality. We conducted a systematic review to determine whether biofeedback hemodialysis (HD) can improve IDH and other outcomes, compared with HD without biofeedback.

Methods. Data sources included the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and ISI Web of Science. We included randomized trials that enrolled adult patients (>18 years) with IDH or extracellular fluid expansion and that used biofeedback to guide ultrafiltration and/or dialysate conductivity. Two authors assessed trial quality and independently extracted data in duplicate. We assessed heterogeneity using I². We applied the GRADE framework for rating the quality of evidence.

Results. We found two parallel-arm randomized controlled clinical trials and six randomized crossover trials meeting inclusion criteria. All trials were open-label and at least four were industry-sponsored. Studies were small...