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Improvement of bone and mineral parameters related to adynamic bone disease by diminishing dialysate calcium

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Abstract

Background: The existence of adynamic bone disease (ABD) as most prevalent form of renal osteodystrophy in recent years and its reduced ability to handle an exogenous calcium load has implied a higher risk for vascular and soft-tissue calcifications. The effect of low dialysate calcium (LCD) on parathyroid hormone (PTH) secretion in ABD patients has not yet sufficiently been clarified. This randomized, prospective study aimed to compare the effects of LCD and high calcium dialysate (HCD) on the evolution of bone and mineral parameters related to ABD in dialysis patients.

Methods: 52 out of 60 patients with predialysis intact PTH < 100 pg/ml completed this study and were equally distributed over LCD (1.25 mmol/l) or HCD (1.75 mmol/l) treatment. The duration of the study was 6 months and the only peroral phosphate binder administered was calcium carbonate. Total and ionised calcium were measured monthly in serum before and after dialysis while serum parameters relevant to bone were measured at the enrollment and at 3-month intervals.

Results: There were no differences in predialysis mean phosphate or calcium × phosphorus product (Ca × P). The most common side effects of both treatments were comparable. Hypotension occurred in 16% and 17% and cramps in 6% and 8% of the dialysis sessions, in the HCD and LCD group, respectively.

The groups did not differ in the mean tCa before dialysis, but this parameter was significantly higher in the HCD group vs. LCD at the end of dialysis (2.59±0.18 vs. 2.44±0.19 mmol/l; $p<0.01$). The patients of the HCD group also had a significantly higher mean iCa both before (1.08±0.05 vs. 1.04±0.06 mmol/l; $p=0.02$) and at the end of dialysis (1.18±0.04 vs. 1.48±0.04 mmol/l; $p<0.01$). There were no differences within the LCD group between baseline and end of dialysis treatment values of tCa and iCa. However, the mean tCa and iCa were markedly increased at the end of dialysis in the HDC group [2.40±0.21 vs. 2.59±0.18 mmol/l ($p<0.01$); 1.08±0.05 vs. 1.18±0.04 mmol/l ($p<0.01$)].

Mean serum levels of iPTH and total alkaline phosphatase in the LCD group were increased at 3 months and at the end of the study compared with the baseline levels [(38.6±22.9 vs. 63.3±46.0 vs. 78.6±44.7 pg/ml); (59.5±18.7 vs. 75.9±26.7 vs. 84.0±35.4 U/l)], respectively, and bone alkaline phosphatase increased also only after 6 months of treatment (23.4±7.3 U/l vs. 35.6±22.3). The bone markers in the HCD group did not change. At the end of the study all bone parameters in the LCD group were significantly higher than in the HCD group.

Conclusion: There was an evolution towards parameters reflecting higher bone turnover in patients treated with dialysate calcium of 1.25 mmol/l, probably by prevention of a positive calcium balance and enabling sustained stimulation of PTH secretion. Hence, LCD might be considered a valuable therapeutic option for ABD patients.

Keywords: Dialysis; Ionised calcium; Parathyroid hormone; Low dialysate calcium concentration; Adynamic bone disease

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Introduction

The abnormalities in bone histology in patients with chronic kidney disease (CKD), known as renal osteodystrophy (ROD), can be observed early in the course of the disease. The spectrum of ROD in dialysis patients has been studied thoroughly and the prevalence of the various types of renal bone disease changed over the years with adynamic bone disease (ABD) as most prevalent bone lesion within the dialysis population in the last two decades [1]. This type of ROD was first found in association with high bone aluminum accumulation [2]. Other factors that are important for the development of ABD consist of malnutrition, male gender, diabetes mellitus and advanced age [3–5]. Calcium-based phosphate binders, particularly when used in combination with vitamin D analogues, may result in over-suppression of parathyroid hormone (PTH) which might as such result as well in ABD [6]. However, it was observed that most of the cases with ABD were found in patients with "relative" hypoparathyroidism, i.e. PTH levels that were significantly lower than those noted in renal failure patients with other types of ROD, but still higher than in subjects with normal renal function [7]. The possible explanation might be the bone "resistance" of uremic patients to the stimulatory effect of PTH because of a down-regulation of its receptor and dysfunction of osteoblasts [8] as well as the accumulation and the effect of uremic toxins on the parathyroid–bone axis [9,10].

Bone biopsy is considered as the gold standard for ROD diagnosis [11], but various biochemical markers have been evaluated over the last decades, with hope that they could replace this invasive diagnostic tool. Nowadays most of these markers reach a satisfactory diagnostic accuracy, although they are not yet considered accurate enough to replace bone histomorphometry [12].

The existence of ABD as most prevalent form of ROD in recent years and its reduced ability to handle an exogenous calcium load has implied a higher risk for extra-osseous calcifications [13]. Since dialysate should contain calcium as one of the essential electrolytes, and since its concentration may fluctuate along the sessions, a suitable dialysate calcium concentration is important as a therapeutic option for ABD patients.

Numerous investigators have suggested that using low-calcium dialysate (LCD) might benefit HD patients at large, allowing a larger dose of calcium binders to control hyperphosphatemia and secondary hyperparathyroidism, and avoiding hypercalcemia and excessive PTH suppression even with high doses of vitamin D treatment [14,15]. Similar data on populations with ABD are needed, since the response in ABD should not necessarily be the same as in the overall HD population because of the presence of severely suppressed bone. The few studies in this context were, however, either uncontrolled [16,17], or restricted to a diabetic population with inclusion criteria not conforming with ABD (PTH < 300 pg/ml) [18]. Hence, the effect of LCD on PTH secretion in ABD patients has not yet sufficiently been clarified. In spite of extensive development of guidelines in the area of bone and mineral metabolism [19], there are still no evidence based recommendations on desired dialysate calcium as a possibility for treatment of ABD.

The aim of the present study was to: i) compare the effects of low (LCD) and high dialysate calcium (HCD) concentration on the evolution of parameters reflecting adynamic bone disease in dialysis patients; ii) to evaluate the safety of LCD treatment.

Patients and methods

Out of the 170 patients in our unit who were all treated by haemodialysis (HD) for 3 × 4 h per week with low flux polysulfone or hemophan membranes and with standard maintenance bicarbonate (34 mmol/l) dialysate containing 1.75 mmol/l calcium, the 60 patients characterized by biochemical parameters compatible with ABD were selected for this randomized, comparative study. The dialysate was highly purified by reverse osmosis treatment in the absence of aluminum exposure. Dialysate flow was set at 500 ml/min, blood flow at 250–280 ml/min and standard dialysate temperature at 37.0 °C. Ultrafiltered volume was measured indirectly as a difference between pre- and post-dialysis body weight.

The key inclusion criterion was a concentration of intact parathyroid hormone (PTH) < 100 pg/ml (corresponding to the cut-off value for ABD according to K/DOQI guideline 13C) at the last two regular laboratory evaluations within 6 months prior to the commencement of the study.

According to the design of the study, an equal number of patients ($n = 30$) were randomly assigned either to the LCD (1.25 mmol/l) group or to the group continuing on the HDC (1.75 mmol/l) treatment. Fifty-two patients completed the study. Patients were excluded from the study if their dialysis schedule had to be modified from the baseline protocol. Four patients in each group dropped out, essentially because of symptoms compatible with hemodynamic problems (hypotension and cramps) each time exacerbated by excessive ultrafiltration needs. Mean patient age was 59.2 ± 11 years and they had received HD for a mean period of 67.5 ± 47.6 months (range: 15–228).

No preset limit was applied to serum calcium and phosphate levels nor was there any restriction in concomitant erythropoietin therapy. None of the patients had ever received aluminum-containing phosphate binders or vitamin D analogues, in view of the ABD status of all included patients. By definition, also no vitamin D analogues were administered during the course of the study. Calcium carbonate was used as only peroral phosphate binder since commencement of dialysis treatment.

Clinical data on the patients were recorded at the moment of inclusion [age, type of chronic kidney disease, start of dialysis treatment and duration, gender, presence of diabetes and intake of medication]. Adverse events were monitored throughout the study. Intra-dialytic hypotension was defined as a decreased blood pressure by more than 20% from pre-dialysis, characterized clinically by malaise, fatigue and/or loss of consciousness necessitating medical intervention [20]. The duration of the study was 6 months. Blood samples were taken during the first session of the week (morning or afternoon shift), at the beginning of the study (baseline) and at 3-month intervals for determination of serum parameters relevant to bone. Intact PTH was measured using the Nichols IRMA kit (Nichols Institute, San Juan Capistrano, CA) and bone alkaline phosphatase (BAP) was determined by electrophoresis using the ISOPAL-kit. Total alkaline phosphatase, calcium and phosphate were measured by standard automated techniques. Total and ionised serum calcium were measured monthly before and after dialysis at the first session of the week. The data from the dropped out patients were not taken into the database for the primary statistical analysis, but data on hemodynamics were submitted to secondary analysis this time including the dropped out patients.

Descriptive statistics included mean values ± S.D. for continuous data, and percentage for categorical data. In the statistical analysis, ANOVA was undertaken as pre-test, followed by a post-test only in case of significance. Between the groups, comparison was performed by unpaired Student's *t*-test analysis. Categorical data were compared by the chi-square test. A p value < 0.05 was considered to be significant at a two-tailed level. The Ethical Committee of the Medical Faculty at the University of Skopje (Macedonia) approved the study protocol.