Adynamic Bone Disease - Clinical Outcome of the Treatment with Different Dialysate Calcium Concentration

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Introduction

The abnormalities in bone histology in patients with chronic renal failure (CRF), known as renal osteodystrophy (ROD), can be observed early in the course of the disease. Over the last decades 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 (1). In recent years, adynamic bone disease (ABD) has become the most prevalent bone lesion within the dialysis population. This type of ROD was first found in association with high bone aluminum accumulation (2). Other factors that might have played an important role in development of ABD consist of malnutrition, male predominance, diabetes mellitus and advanced age (3-5). Calcium-based binders, particularly when used in combination with vitamin D analogues, may result in over-suppression of PTH (6). However, it was observed that most of the cases with ABD were found in patients with "relative" hypoparathyroidism, i.e parathyroid hormone (PTH) levels that are 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).

Bone biopsy is considered as the gold standard for ROD diagnosis (8), but various biochemical markers have been most frequently evaluated over the last decades. Predominantly, the investigators measure intact parathyroid hormone (iPTH), total or ionized serum calcium (Ca), phosphate (P), alkaline phosphatase (AP), vitamin D status and some markers of either bone formation [bone alkaline phosphatase (BAP), osteocalcin (OC)] or bone resorption [(deoxy-) pyridinolines (DPYD, PYD)]. Most of these markers reach a high enough diagnostic performance to substitute bone histomorphometry.

Disturbances of calcium-phosphate (Ca-P) metabolism in CRF play an important role not only in bone disease but also in soft tissue calcification, with an increased risk of vascular calcification, arterial stiffness, and worsening of atherosclerosis, linked to an increased mortality in a large number of dialysis patients. On the other side, the use of calcium salts for phosphate binding is complicated by the development of hypercalcemia and an increased risk of metastatic calcifications in a substantial fraction of patients particularly those taking vitamin D analogues and those with adynamic bone disease (6). Moreover, ABD patients show a reduced ability to handle an exogenous calcium load, and have a more sustained hypercalcemia, implying a higher risk of extra-osseous calcifications. Hence, a suitable dialysate calcium concentration is important and must take into consideration the medical therapy and the calcium balance on an individual patient basis.

Despite all the controversy, numerous investigators have suggested that using low-calcium dialysate (LCD) might benefit HD patients, allowing a larger dose of calcium to control hyperphosphatemia and avoiding excessive PTH suppression (9,10). Nevertheless, the information about the stimulating effect of LCD on PTH secretion is not yet clarified.

The aim of the study was to compare the effects of low (LDC) and high dialysate calcium (HDC) concentration on the evolution of adynamic bone disease in dialysis patients.

Methods

In this open-label study, 52 ABD presumed patients on maintenance bicarbonate haemodialysis (HD) for 12 hours per week, with low flux polysulphone or hemophane membrane were included. The key inclusion criteria was concentration of parathyroid hormone (PTH)<100 pg/ml and bone alkaline phosphatase (BAP)<37 U/L. An equal number of patients (n=26) were randomized to LCD (1.25 mM) and HDC (1.75 mM) concentration. No preset limit is applied to serum calcium and phosphate levels neither any restriction of concomitant vitamin D or erthropoietin therapy. The only phosphate binder to be used was calcium carbonate. The duration of the study was 6 months. Clinical data on the patients will be recorded at the moment of inclusion (age, type of chronic kidney disease, start of dialysis treatment and duration, gender, blood pressure (before the dialysis session), diabetes, smoker, treatment with erthropoietin and dose, type of vascular access, intake of medication). Adverse events were monitored throughout the study and 4 (HDC) patients were discontinued from the study upon investigator's decision. Blood samples were taken at the enrollment and at 3 months interval for determination of a series of serum parameters relevant to bone using the appropriate kits and methodologies. Total and ionized calcium were measured monthly in serum before and after dialysis.

Descriptive statistics will include mean values ± SD for continuous data, and percentage for categorical data. Between the groups comparison will be performed by Student's t - test analysis. Categorical data will be compared by the chi-square test.

Results

After randomized allocation to either LCD or HDC, 30 patients in each group initiated the study. As a consequence of the expected side effects of the treatment with LCD (hypotension and cramps), 4 patients were excluded from the study (LCD group). Fifty-two patients completed the study. 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 months). The LCD and HCD group did not differ significantly in terms of age (LCD: 61 ± 11.8 years vs HCD 57.3 ± 9.9 years), male gender (n=14 in each group) and time on HD (LCD: 74.7 ± 48.2 months vs HCD 59.3 ± 46.7 months). Fourteen patients had diabetes (LCD: n=8, HCD: n=6).

The inclusion criteria in the present study were even more restrictive than those reported to be a good marker of ABD in HD patients (PTH<100 pg/ml and BAP<37 U/L) (Coutoneye 1996 Low BAP). Thus, the design of the study aimed to assess the possibility for treatment of ABD. In contrast to some reports, the treatment with LCD was not accompanied with a negative calcium balance, since there was no change in iCa and tCa during dialysis (9).

However, it should be mentioned that the mean iCa levels in LCD group were continously sustained below the referent range of the lab (1.1 - 1.3 mmol/l). These findings suggest that prevention of net calcium influx, rather than its negative balance, might be responsible for the increase in PTH. The similar pattern of increased markers of bone formation (BAP and TAP) in LCD group has been observed over the whole study period. Hence, an increase in bone formation rate might improve the buffer capacity of the bone for handling of calcium influx, thus preventing extraskeletal and cardiovascular calcifications.

**Conclusion**

In conclusion, there was an evolution towards higher bone turnover in patients treated with dialysate calcium of 1.25 mM, probably by preventing a positive calcium balance and causing repetitive stimulation of PTH secretion in each dialysis. The treatment was safe and without any major adverse effects. Hence, this might be considered a valuable treatment for ABD patients, although this rather beneficial and not harmful effect should be confirmed in a long-term evaluation.

**Key words**: dialysis, ionised calcium, parathyroid hormone, low dialysate calcium concentration, adynamic bone disease.

**Reference**


