Low-Calcium Dialysate Stimulates Parathormone Secretion and Its Long-Term Use Worsens Secondary Hyperparathyroidism¹

Elvira Fernández, Mercè Borràs, Beatriz Pais, and Jesús Montoliu²

E. Fernández, M. Borràs, B. Pais, J. Montoliu, Nephrology Service, University Hospital Amor de Vilanova, and Departments of Medicine and Surgery, University of Lleida, Lleida, Spain


ABSTRACT

The long-term clinical effects of the use of a low calcium concentration in the dialysate are largely unknown. For this reason, the influence of low-calcium dialysate on parathyroid hormone (PTH) secretion in hemodialysis patients and its long-term effect on the severity of secondary hyperparathyroidism were studied. In 35 hemodialysis patients, the dialysate calcium concentration was lowered from 1.75 to 1.25 mmol/L. Twelve months later, serum iPTH levels increased significantly from 18.6 to 33.2 pmol/L and so did alkaline phosphatase levels, from 210 to 330 IU/L, without significant changes in serum calcium or phosphorus levels. Hemodialysis with low-calcium dialysate (1.25 mmol/L) induced a net calcium loss in 10 patients, without modifications in ionized serum calcium levels. In addition, mean serum iPTH increased 20% over baseline levels, reaching the maximal level at 30 min after the start of hemodialysis with low-calcium dialysate. In contrast, mean serum iPTH levels drop dramatically at 30 min of hemodialysis with high-calcium dialysate (1.75 mmol/L). It was concluded that low-calcium dialysate worsens secondary hyperparathyroidism in hemodialysis patients, probably by inducing a negative calcium balance and causing repetitive stimulation of PTH secretion in each dialysis. The maintenance of normal serum calcium levels could be due to PTH-induced calcium mobilization from bone.

Key Words: Low-calcium dialysate, secondary hyperparathyroidism

¹ Received July 29, 1994. Accepted March 28, 1995.
² Correspondence to: Dr. J. Montoliu, Nephrology Service, Hospital Amor de Vilanova, Rovira Roura 80, 25006 Lleida, Spain.

In the early days of dialysis, a 1.25 mmol/L dialysate calcium concentration was frequently used. It soon became apparent that this dialysate solution could decrease ionized serum calcium and aggravate secondary hyperparathyroidism (1–5). To prevent these complications, dialysate calcium concentration was then switched to 1.75 mmol/L and has remained so for many years (6).

More recently, however, there has been a tendency to substitute aluminum hydroxide by calcium salts as phosphate binders. This, as well as the widespread use of oral and intravenous calcitriol and bicarbonate dialysis, has favored the development of hypercalcemia and soft tissue calcifications in hemodialysis patients. To counteract this, there is again a trend to use a low calcium concentration in the dialysate (7–10).

The long-term clinical effects of such a new treatment policy, in these times of calcium salts as phosphate binders, oral and intravenous calcitriol, and bicarbonate dialysis, are largely unknown (11). For this reason, we undertook this study in order to evaluate the influence of a low-calcium dialysate on parathyroid hormone (PTH) secretion in hemodialysis patients and its long-term effect on the severity of secondary hyperparathyroidism.

METHODS

The study was divided in two parts. In the first part, we studied the long-term effect of low-calcium dialysate. In the second part, we studied the intradialysis effect of low-calcium dialysate.

Long-Term Effect of Low-Calcium Dialysate

We studied 35 patients, 20 men and 15 women, aged 17 to 75 yr (average, 58 yr) who had been on hemodialysis for a mean of 42 ± 14 months (± SD). In these patients, the dialysate calcium concentration was lowered from 1.75 to 1.25 mmol/L, and aluminum hydroxide was simultaneously substituted by calcium carbonate as a phosphate binder. The calcium carbonate dosage ranged from 3 to 6 g/day. The dialysate magnesium concentration (0.5 mmol/L) was unchanged during the study. The 20 patients with serum iPTH levels higher than 15 pmol/L were receiving oral calcitriol, and this medication and its dosage (0.25 to 0.50 μg after each hemodialysis) were kept constant during the study. Similarly, the hemodialysis schedule and type of dialyzer remained unchanged during the study period. The mean ultrafiltration volume was 578 mL/h (range, 300 to 750 mL/h).

Immediately before and 6 and 12 months after the dialysate change, the following data were measured: total serum
calcium, serum phosphate, serum alkaline phosphatase, and serum iPTH (normal range, 1.2 to 5.6 pmol/L). Biochemical values were measured with an autoanalyzer. Serum iPTH was measured by a two-site chemiluminometric immunoassay (Magic Lite; Ciba Corning Diagnostics Corp., Medfield, MA). Previous studies have validated the correlation of this test with the immunoradiometric assay. For the statistical study, we used the average values of two measurements with a 3-month interval before and after the dialysis change.

Intradialysis Effect of Low-Calcium Dialysate

Of the 35 patients monitored for 1 yr, we selected 10 because of significant worsening of secondary hyperparathyroidism. In them, serum iPTH went from 17.8 pmol/L before to 62.1 pmol/L after the dialysis change.

In our laboratory, the method for measuring dialysate calcium has a 4% variation coefficient. Dialysate samples for each patient were measured with the same autoanalyzer calibration.

The calcium balance at the beginning and the end of a 4-h hemodialysis with low-calcium dialysate was calculated. The mean ultrafiltration volume was 660 ± 76 mL/h, similar to what it had been during the last month of the previous study period (590 mL/h). At the beginning and the end of each hemodialysis, ultrafiltration rate, serum ionized calcium, and total serum calcium at the dialyzer inlet and outlet were measured. Fluid removal was kept at a constant rate throughout the hemodialysis procedure by use of a machine with ultrafiltration volumetric control (Monitrall; Hospal, Basel, Switzerland), and the dialysate flow was adjusted to 500 mL/min.

Calcium mass transfer (in millimoles per minute) was calculated according to the formula (12):

\[
\text{Calcium mass transfer} = \text{Di} - \text{Do}
\]

where \(\text{Di}\) = total calcium content at dialyzer inlet and \(\text{Do}\) = total calcium content at dialyzer outlet, and

\[
\text{Di} = \text{DCa} \times \text{QD}
\]

\[
\text{Do} = \text{DCa} \times (\text{QD} + \text{QUF})
\]

where \(\text{DCa}\) = calcium concentration in dialysate (in milligrams per milliliter); \(\text{QD}\) = dialysate flow (in milliliters per minute); and \(\text{QUF}\) = ultrafiltrate flow (in milliliters per minute).

We also compared serum ionized calcium and serum iPTH changes during hemodialysis in four patients using a low-dialysate calcium concentration (1.25 mmol/L) and in another four patients using a high-dialysate calcium concentration (1.75 mmol/L).

The hemodialysis prescription and ultrafiltration rate were the same as previously described. Mean baseline serum iPTH levels were not significantly different in the patients using low- or high-calcium dialysate (20 ± 0.7 versus 25 ± 0.8 pmol/L, respectively; \(P = \) not significant [NS]). Blood samples for serum iPTH and ionized calcium levels (measured with a Ciba Corning 634 autoanalyzer) were drawn from the arterial line at the beginning of hemodialysis and then every 15 min in the first hour and every 30 min thereafter until the end of the session. Results are expressed as means ± SD. A t test for paired data was used for statistical analysis.

RESULTS

Long-Term Effect of Low-Calcium Dialysate

Six months after lowering the dialysate calcium concentration, serum iPTH levels increased from 18.6 ± 5 to 22.5 ± 8 pmol/L, but this difference was not statistically significant. However, the serum iPTH increase was larger 12 months after the dialysate change, reaching a value of 33.2 ± 7 pmol/L (\(P < 0.001\) with respect to baseline values). Similarly, serum alkaline phosphatase levels increased from 210 ± 26 to 250 ± 24 IU/L at 6 months (\(P =\) NS) and to 330 ± 31 IU/L at 12 months (\(P < 0.001\) with respect to baseline) (Figure 1).

However, total serum calcium and phosphate levels remained unchanged (2.37 ± 0.6 versus 2.4 ± 0.2 at 6 months versus 2.3 ± 0.6 mmol/L at 12 months and 1.96 ± 0.06 versus 2 ± 0.08 at 6 months versus 2.06 ± 0.06 mmol/L at 12 months, respectively; \(P = \) NS). For 26 patients (74.2% of the total group), the iPTH increase was 20% or higher over the baseline values.

Intradialysis Effect of Low-Calcium Dialysate

Mean calcium loss in the dialysate and the ultrafiltrate was greater at the beginning than at the end of the hemodialysis with low-calcium dialysate (0.32 ± 0.07 and 0.1 ± 0.05 mmol/min, respectively). If a continuous decline of calcium mass transfer is assumed during hemodialysis, the total loss of calcium can be calculated as the mean between the two values (50.4 mmol/session). Despite this negative balance, serum ionized calcium levels remained unchanged (1.1 ± 0.0 versus 1.2 ± 0.0 mmol/L; \(P = \) NS) (Figure 2).

Figure 3A shows that in the group of patients dialyzed with low-calcium dialysate, the mean serum iPTH increase reaches its maximum level 30 min after the start of hemodialysis, with a 20% increase over

![Figure 1. Changes in serum iPTH levels and serum alkaline phosphatase after 6 and 12 months of treatment with low-calcium dialysate (1.25 mmol/L).](image-url)
baseline levels \(P = 0.05\) by t test), and then declines progressively until the end of the procedure. Serum ionized calcium levels remain constant throughout low-calcium dialysis. In contrast, Figure 3B shows that in the group of patients dialyzed with high-calcium dialysate, mean serum iPTH levels drop dramatically at 30 min and then remain suppressed until the end of the session. At the same time, serum ionized calcium levels increase progressively during dialysis with high-calcium dialysate (Figure 3B).

**DISCUSSION**

In recent years, there has been a tendency toward the use of low-calcium dialysate, to compensate for the use of high-dose calcitriol therapy and calcium salts as phosphate binders (12). The long-term effects of this type of treatment are unknown, but our results indicate that it can worsen secondary hyperparathyroidism. One year after lowering the dialysate calcium, PTH levels and serum alkaline phosphatase levels increased significantly in our patients, as a result of parathyroid gland stimulation. Serum calcium and phosphorus did not change. Other potential factors implicated in PTH secretion, such as the calcitriol dose, were not modified and therefore can be ruled out as contributory to the parathyroid stimulation. Results similar to ours have been recently reported by Malberti et al. (13). They observed that the use of a dialysate calcium concentration of 1.51 mmol/L was associated with loss of calcium and worsening of bone disease in dialysis patients. However, Slatopolsky et al. (14) and Oettinger et al. (15) observed a slight decrease in serum PTH levels when using a 1.25 mmol/L dialysate calcium concentration and calcium carbonate as a phosphate binder. Several reasons can be offered to explain the differences between these studies and our results. Firstly, in the studies of both Slatopolsky et al. and Oettinger et al., a slight increase in serum calcium was observed, whereas serum calcium did not change in our study. Therefore, in those two articles (14,15), the slight decrease in serum PTH can be at least partially explained by the increase in serum calcium. Second, observation time can also influence the results. Their studies were run for 6 to 7 months only, and when we look at our 6-month results, no significant increase in serum PTH levels could be observed either; we had to wait until a 12-month follow-up to observe a significant increase in serum PTH and alkaline phosphatase levels. It is conceivable that an extended observation period is necessary to document worsening of secondary hyperparathyroidism. Finally, in some of the former studies (14,15), older and less sensitive PTH assays were used, thus providing another possible explanation for the discrepancy with our results using a modern PTH assay. Our results are also consistent with the extensive body of knowledge indicating that in chronic renal failure, supraphysiologic levels of serum calcium are required to offset PTH secretion (9).

The worsening of secondary hyperparathyroidism...
when using low-calcium dialysate can be explained by the repetitive stimulation of parathyroid secretion during dialysis. We have shown that dialysis with a low-calcium dialysate induces a net calcium loss, despite the fact that ionized serum calcium levels do not change. This loss of calcium is associated with a marked increase in serum iPTH levels, which are maximal at 30 min of hemodialysis. Again, ionized calcium levels do not change throughout dialysis. Because low calcium-induced PTH secretion occurs very rapidly, as does PTH-induced calcium mobilization from bone, and taking into account the very short metabolic half-life of PTH, we can offer the following hypothesis to explain this sequence of events: loss of calcium during dialysis would cause a slight decrease in ionized serum calcium, which would stimulate PTH secretion; this in turn would provoke calcium mobilization from bone, the net result being that serum ionized calcium levels are kept constant and minimal changes go undetected by the current methods of clinical measurement. Calcium loss is superior at the beginning of hemodialysis despite keeping a constant ultrafiltration rate. The explanation for this is not totally clear at the moment, but it is possible that because in the dialysate we measure total calcium (ionized plus phosphate bound), phosphate-bound calcium removal would be higher at the beginning of hemodialysis.

This is in contrast with the clear increase in ionized serum calcium levels and subsequent PTH suppression that occur during dialysis with a high-dialysate calcium. It is presently unknown if this worsening of secondary hyperparathyroidism by low-calcium dialysate can be prevented by using higher calcitriol doses, but in any case, the pharmacokinetics of oral or intravenous calcitriol should be taken into account in order to obtain the maximum effect during hemodialysis session.

In summary, we have demonstrated that, in the long term, dialysis with low-calcium dialysate worsens secondary hyperparathyroidism in uremic patients, probably by inducing a negative calcium balance during hemodialysis and causing repetitive stimulation of PTH secretion. Further studies are needed to know if this can be prevented by modifications in the dose or mode of administration of calcitriol or other changes in the current policy of the treatment of renal osteodystrophy.

ACKNOWLEDGMENTS
This study has been supported by a grant from La Puerta to the University of Lleida. The authors thank the Biochemistry Service and particularly Drs. M.C. Rivas and G. Cao for their cooperation.

REFERENCES