Assessment of calcium balance in patients on hemodialysis, based on ionized calcium and parathyroid hormone responses

Anneke Bech 1, Louis Reichert 1, Darryl Telting 2, Hans de Boer 1

ABSTRACT

Background: Identification of the underlying causes of secondary hyperparathyroidism (SHPT) in individual patients on hemodialysis (HD) is hampered by the lack of clinically reliable information on calcium balance. The aim of this study was to assess calcium balance during HD sessions with a method that is applicable in day-to-day practice.

Methods: Plasma ionized calcium (pCa2+) and parathyroid hormone (PTH) were measured at the beginning and end of HD to evaluate calcium fluxes in 23 patients on a dialysate calcium (DCa) concentration of 1.25 mmol/L.

Results: HD with a DCa of 1.25 mmol/L caused a decrease in pCa2+ from 1.15 ± 0.01 mmol/L to 1.09 ± 0.01 mmol/L (p<0.0001) and increased plasma PTH from 26.7 ± 1.8 pmol/L to 37.0 ± 2.9 pmol/L (p<0.0001). The changes in pCa2+ were inversely related to the predialysis pCa2+ levels (R² = 0.86, p<0.001). Patients with a predialysis pCa2+ >1.06 mmol/L had a calcium efflux, whereas those with a predialysis pCa2+ <1.06 mmol/L had a calcium influx during HD.

Conclusion: The results suggest that measurement of pCa2+ and PTH at the beginning and the end of HD provides useful information about calcium fluxes in individual patients. Further validation of this approach is warranted.

Key words: Dialysate calcium, Hyperparathyroidism, Ionized calcium, Parathyroid hormone, Renal failure

INTRODUCTION

Accurate assessment of calcium balance in patients on hemodialysis (HD) is crucial. A negative calcium balance can cause hemodynamic instability, muscle cramps, epileptic attacks, secondary hyperparathyroidism (SHPT) and loss of bone (1, 2). A positive calcium balance may lead to hypercalcemia, vascular calcification and increased cardiovascular morbidity and mortality (3). Concerns about the adverse cardiovascular effects of a positive calcium balance have led many nephrologists to reduce the dialysate calcium (DCa) concentration from 1.75 to 1.25 mmol/L, and sometimes even lower (4, 5). The most recent guideline on chronic kidney disease recommends a DCa between 1.25 and 1.50 mmol/L; however, it does not define what DCa would be optimal under various circumstances in individual patients (6).

A zero calcium balance in patients on HD is very difficult to achieve because of the many factors that are involved. The classical balance method that requires quantification of oral intake, fractional intestinal absorption, urinary, fecal and cutaneous calcium loss and the degree of calcium exchange during HD is not feasible in day-to-day practice (7). We suggest that a simpler approach may suffice to improve the monitoring of calcium balance in patients on HD. It is based on the measurement of parathyroid hormone (PTH) responses to HD-induced changes in plasma ionized calcium (pCa2+). According to our hypothesis, measurement of pCa2+ and PTH at the beginning and end of HD should provide information about calcium fluxes during HD as well as between HD sessions. This information is vital to assess
a patient’s calcium balance and to adjust treatment therapy on a rational basis. HD-related calcium exchange is primarily based on diffusion driven by Ca2+ concentration gradients between plasma and dialysate. A second mechanism is calcium transport by convection – i.e., calcium transport through the dialysis membrane as part of the fluid exchange during ultrafiltration (4). Quantitatively, diffusion is the most important mechanism. It is a function of total dialysate volume, DCa concentration and pCa2+ (4, 8). It is well established that a low DCa of 0.75 mmol/L will cause a calcium efflux from the extracellular fluid (ECF) into the dialysate, whereas a high DCa (1.50 or 1.75 mmol/L) will cause a calcium influx (9). It is commonly believed that a DCa of 1.25 mmol/L maintains a zero calcium balance; however, this notion is not well founded. Some balance studies have reported a calcium influx whereas others observed a calcium efflux (1, 2, 4, 9-11). To date, there is no satisfactory explanation for these apparently conflicting results. The present study was triggered by observations in a single patient on daytime HD with a DCa of 1.25 mmol/L (Ca-1.25 dialysate) who had developed severe SHPT that was very difficult to control. Repeated measurements of pCa2+ and PTH at the beginning and end of HD revealed a consistent pattern characterized by a major decrease in pCa2+ and a concomitant large rise in serum PTH during HD. This strongly suggested that the Ca-1.25 dialysate was associated with a chronic calcium efflux and that this had induced severe SHPT. This unexpected observation raised the question of whether a negative intradialytic calcium balance on a DCa of 1.25 mmol/L might be more common than previously thought. As 80% of our hospital’s HD population was being treated with a Ca-1.25 dialysate, such a finding could have major clinical implications. Therefore, it was decided to explore this issue further, and repeated measurements of predialysis and postdialysis pCa2+ and PTH levels were performed in another 23 patients during HD with a DCa of 1.25 mmol/L. We hypothesized that, with an intact Ca2+/PTH feedback loop, the direction and magnitude of changes in plasma PTH levels might reflect the clinical importance of calcium exchange during HD in individual patients.

**Patients and Methods**

**Patients**

Predialysis and postdialysis blood samples were taken from 23 patients on daytime HD with a Ca-1.25 dialysate, during 3 consecutive sessions. The investigation was carried out according to the regulations of the hospital’s ethics committee, and all patients gave their consent. All were in the care of a single nephrologist (L.R.), and selection was based on the criteria that they had to be on a DCa of 1.25 mmol/L for at least 6 months and that dialysis method and medication were not changed during the observation period. HD was performed with a cellulose triacetate filter. The Ca-1.25 dialysate contained calcium 1.25 mmol/L, HCO3− 32 mmol/L and Mg 0.5 mmol/L. Mean session time, ultrafiltration rate and ultrafiltration volume were 3.0 ± 0.1 hour/session, 568 ± 75 ml/hour and 1,717 ± 254 ml/session, respectively.

**Methods**

Plasma Ca2+, pH, bicarbonate and base excess were measured by blood gas analyzer using ion-selective electrodes (OMNI Roche, Mannheim, Germany). Plasma phosphate, magnesium and alkaline phosphatase were measured with standard laboratory tests (Modular Analytics P800; Roche Diagnostics, Mannheim, Germany). Serum intact PTH was measured by a solid-phase, 2-site chemiluminescent enzyme-labeled immunometric assay (DPC, Los Angeles, CA, USA), with intra- and interassay coefficients of variation of <6% and <9%, respectively. 25-Hydroxyvitamin D (25(OH)D3) was measured with a direct competitive chemiluminescence immunoassay (Diasorin Inc., Stillwater, MN, USA). Serum 1,25-dihydroxyvitamin D (1,25(OH)2D3) was measured by radioimmunoassay (Immunodiagnostic Systems GmbH, Frankfurt am Main, Germany).

**Statistical analysis**

Results are shown as mean values ± standard error of the mean (SE). The paired Student’s t-test was used to compare predialysis and postdialysis data. Correlations between data were studied by linear or polynomial regression analysis. A p value <0.05 was considered statistically significant.

**Results**

General patient characteristics, dialysis method and medication use are summarized in Table I. The biochemical changes induced by HD are summarized in Table II. The mean pCa2+ level decreased from 1.15 ± 0.01 mmol/L to 1.09 ± 0.01 mmol/L (p<0.0001), plasma phosphate decreased from 1.67 ± 0.14 mmol/L to 0.75 ± 0.05 mmol/L (p<0.0001), whereas mean PTH concentration increased from 26.7 ± 1.8 pmol/L to 37.0 ± 2.9 pmol/L (p<0.0001). Plasma Mg ranged from 0.73 to 1.40 mmol/L before dialysis and from 0.70 to 1.23 mmol/L after dialysis. Plasma bicarbonate ranged from 18.4
TABLE I
GENERAL PATIENT CHARACTERISTICS, DIALYSIS METHODS AND MEDICATION USE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SE</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>Sex, male</td>
<td>13</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>Time on dialysis, months</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>Duration dialysis, hours</td>
<td>2.95 ± 0.01</td>
</tr>
<tr>
<td>Blood flow, ml/min</td>
<td>299 ± 8</td>
</tr>
<tr>
<td>Dialysis fluid flow, ml/min</td>
<td>568 ± 24</td>
</tr>
<tr>
<td>Kt/V per dialysis</td>
<td>1.15 ± 0.07</td>
</tr>
<tr>
<td>Cholecalciferol, IU/month</td>
<td>46,750 ± 2,220 (14)</td>
</tr>
<tr>
<td>1a Calcidiol, mg/day</td>
<td>0.51 ± 0.06 (19)</td>
</tr>
<tr>
<td>Calcium carbonate, g/day</td>
<td>1208 ± 199 (10)</td>
</tr>
<tr>
<td>Cinacalcet, mg/day</td>
<td>60 (1)</td>
</tr>
<tr>
<td>Sevelamer, mg/day</td>
<td>5,066 ± 805 (18)</td>
</tr>
<tr>
<td>Lanthanum carbonate, mg/day</td>
<td>2,062 ± 472 (4)</td>
</tr>
</tbody>
</table>

Medications are shown as mean dose ± standard error, and with the number of patients using the medication (in parentheses).

TABLE II
BIOCHEMICAL CHARACTERISTICS OF 23 PATIENTS, BEFORE AND AFTER HEMODIALYSIS

<table>
<thead>
<tr>
<th></th>
<th>Predialysis</th>
<th>Postdialysis</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca²⁺ (mmol/L)</td>
<td>1.15 ± 0.02</td>
<td>1.09 ± 0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PO₄ (mmol/L)</td>
<td>1.67 ± 0.14</td>
<td>0.75 ± 0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mg²⁺ (mmol/L)</td>
<td>1.00 ± 0.05</td>
<td>0.82 ± 0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.01</td>
<td>7.44 ± 0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>21.5 ± 0.7</td>
<td>27.2 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTH (pmol/L)</td>
<td>26.7 ± 1.8</td>
<td>37.0 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Results in mean values ± standard error.
PTH = parathyroid hormone.

Individual changes in plasma pCa²⁺ and PTH during HD are shown in Figure 1. The majority of patients had a decrease in pCa²⁺ during HD, and a concomitant increase in PTH. As shown in Figure 2, the change in pCa²⁺ (ΔpCa²⁺) was inversely related to the predialysis pCa²⁺ level: ΔpCa²⁺ = 0.66 – (0.62 × predialysis pCa²⁺); SEE = 0.024 mmol/L (R² = 0.86, p<0.0001). This regression line indicates that a Ca-1.25 dialysate will not cause a change in pCa²⁺ during HD if the patient’s predialysis pCa²⁺ level = 1.06 mmol/L, suggesting zero calcium balance at this level. It also indicates that a predialysis pCa²⁺ >1.06 mmol/L is associated with a decrease in pCa²⁺ during HD, suggesting an intradialytic calcium efflux. In patients with a predialysis pCa²⁺ <1.06 mmol/L, the Ca-1.25 dialysate induced a rise in plasma pCa²⁺, and this was attributed to a calcium influx from the dialysate into the ECF. This finding suggests that all patients with predialysis pCa²⁺ levels within the normal range will exhibit a calcium efflux, and that the efflux will be greater if predialysis pCa²⁺ levels approach the upper normal limit.

DISCUSSION

The main finding of this study was that a Ca-1.25 dialysate causes a decline in pCa²⁺ in the majority of patients who have normal predialysis pCa²⁺ levels. The magnitude of this decrease was positively correlated with the pCa²⁺ level at the start of HD. For example, patients with a predialysis pCa²⁺ of 1.10 mmol/L will experience a decrease in serum Ca²⁺ of only 0.03 mmol/L, whereas patients with a predialysis pCa²⁺ of 1.30 mmol/L will experience a drop of 0.17 mmol/L (Fig. 2). In a chronic setting, a calcium efflux of this magnitude may result in a major body calcium deficit and severe SHPT, in particular in patients with low calcium intake or poor calcium absorption.
The number of patients we studied was limited, and therefore our conclusions should be regarded as preliminary. However, the results were very consistent and indicate that about a third of patients on HD with a Ca-1.25 dialysate may be at risk to develop HD-induced SHPT. This is an unexpectedly high number that warrants further investigation on a larger scale, taking into account the many other factors that affect calcium balance in HD patients, such as vitamin D status, types of phosphate binders and the use of calcimimetics. The observation that two thirds of the patients did not demonstrate a major rise in PTH during HD suggests that the dialysate calcium concentration was appropriate in their case.

The key question is whether HD-related changes in pCa$^{2+}$ and PTH during HD are reliable indicators of calcium fluxes during HD. Thus far, it is a hypothesis mainly based on theoretical considerations. Changes in pCa$^{2+}$ levels during HD can be caused by an exchange of Ca$^{2+}$ between the blood and the dialysate, or by a redistribution of Ca$^{2+}$. The latter occurs when Ca$^{2+}$ is deposited in bone or soft tissue, or when the binding affinity to albumin is changed by major fluctuations in pH (12). Redistribution of calcium as an explanation for the change in pCa$^{2+}$ is unlikely in the present study. Predialysis pCa$^{2+}$ and phosphate levels were relatively low, which makes extra skeletal deposition of calcium phosphate unlikely. Increased binding of Ca$^{2+}$ to albumin is also unlikely because excessive alkalinization was not observed (Tab. I). Therefore, in the absence of conditions favoring calcium redistribution, we believe that an intradialytic decrease in pCa$^{2+}$ can be interpreted as a calcium efflux, and an increase in pCa$^{2+}$ as a calcium influx.

Calcium fluxes during HD have been quantified by balance studies based on the measurement of calcium appearing or disappearing from the dialysate. Although this method is commonly regarded as the gold standard, its accuracy has never been established. Balance studies with a Ca-1.25 dialysate have produced results varying from an estimated calcium influx of 5.4 mmol/session and a calcium efflux of 0.14-8.1 mmol/session (1, 2, 4, 9). Our data indicate that a Ca-1.25 dialysate causes calcium loss in the majority of patients. Our data also explain that the observed variation and discrepancies in previous balance studies may partly relate to differences in predialysis pCa$^{2+}$ levels (1, 13). We have shown that it is a major factor determining calcium flux direction. Variability in calcium loss by differences in ultrafiltration volume may be another factor.

Measurement of predialysis and postdialysis pCa$^{2+}$ alone is insufficient to understand the physiological importance of a shift in calcium levels in a single patient. The change may occur within the individual’s normal range, or it may exceed the individual’s upper or lower normal limit. An additional signal will be required to indicate whether the change in pCa$^{2+}$ exceeds the patient-specific normal range and whether it might represent a potential risk. This crucial information can be obtained by assessment of the PTH response. The patient-specific pCa$^{2+}$ normal range is determined by the set point of the calcium-sensing receptor (CaSR), and any change in pCa$^{2+}$ exceeding these individual limits is promptly followed by a reciprocal change in PTH secretion (14). The half-life of PTH is less than 5 minutes which makes it an ideal tool to interpret the short-term changes in pCa$^{2+}$ (15). This is illustrated in Figure 3. Fifteen out of 16 patients with predialysis pCa$^{2+}$ levels within the normal range had concordant changes in pCa$^{2+}$ and PTH – i.e., they had a combination of either a decrease in pCa$^{2+}$ and a rise in PTH, or an increase in pCa$^{2+}$ and a fall in PTH. Within this group, two thirds had an increase in serum PTH less than 10 pmol/L, suggesting that the HD-induced changes in pCa$^{2+}$ were not causing a major disturbance in calcium balance. In contrast, 7 patients (blue lines) had considerably larger responses, with increases in PTH varying between 11 and 45 pmol/L. These were the patients who were probably at risk to develop HD-induced SHPT and who may have needed an increase in dialysate calcium to prevent an excessive rise in PTH. Three patients had discrepant PTH responses – i.e., 2 had a small increase in pCa$^{2+}$ as well as PTH, and 1 had a small decrease in pCa$^{2+}$ and PTH. Further evaluation will be necessary to assess whether these discrepancies are related to inaccuracies as a result of intra-assay and inter-assay variation.
Quantitatively, the degree of PTH response may vary between individuals. It has been shown previously that predialysis pCa2+ is lower and PTH is higher in HD patients with SHPT than in those with adynamic bone disease, and that the magnitude of the PTH response to changes in pCa2+ depends on the type of renal osteodystrophy (16). In patients with SHPT, a high degree of responsiveness is observed, suggesting that a chronic calcium deficit increases the parathyroid gland’s sensitivity to changes in calcium balance. Conversely, the poorer PTH responsiveness in adynamic bone disease may be explained by the desensitizing effect of a chronically positive calcium balance. The data in the present study are too limited to define which PTH response should be classified as exceeding the normal limit. We set the limit of change at 10 pmol/L, arbitrarily. Although the magnitude of the PTH response is primarily determined by the change in pCa2+ and the overall calcium balance, other factors are also involved. Hyperphosphatemia is known to stimulate PTH secretion (17, 18), whereas hypermagnesemia and 1,25(OH)2D3 suppress PTH secretion (19, 20). Alkalization stimulates PTH release by decreasing pCa2+ (12). In the present study, serum phosphate, magnesium and bicarbonate levels were rather well controlled, with no excessive changes during HD. Therefore, the impact of these factors was probably negligible. Even if there might be some effect on the magnitude of the PTH response, the direction of change in PTH in response to fluctuations in pCa2+ would not be affected.

The most puzzling observation in this study was the finding that a predialysis pCa2+ of 1.06 mmol/L was associated with zero pCa2+ change, suggesting calcium equilibrium between dialysate and blood at this level. We had expected that equilibrium would be reached at a pCa2+ of 1.25 mmol/L – i.e., equivalent to the dialysate calcium concentration of 1.25 mmol/L. To explain this unexpected discrepancy, we reasoned that formation of calcium complexes by partial binding of the dialysate calcium to negative ions added to the dialysate could have led to a decrease of the dialysate Ca2+ level below 1.25 mmol/L. In search of evidence for this hypothesis, we performed a biochemical analysis of the Ca-1.25 dialysate, sampled from a port just before the dialysis filter – i.e., after the dialysate mix with the acetate/bicarbonate solution. This revealed a dialysate total calcium concentration of 1.31 mmol/L, with an actual Ca2+ concentration of only 1.05 mmol/L – i.e., 20% lower than expected. Subsequent analysis of a “1.50” dialysate showed a total calcium of 1.49 mmol/L and an actual Ca2+ of 1.20 mmol/L (20% lower than expected), and analysis of a “1.75” dialysate showed a total calcium of 1.70 mmol/L and an actual Ca2+ concentration of 1.36 mmol/L (20% lower than expected). Apparently, approximately 20% of the calcium is bound in complexes with acetate and/or bicarbonate added to the dialysate at the inflow site, just before the dialysis filter. A subsequent literature search confirmed this finding of a reduced dialysate Ca2+. Previous reports have noted binding percentages of 12%-17% (5, 10, 12, 21). This clearly explains that calcium equilibrium occurs at a lower concentration than suggested by the dialysate total calcium concentration. The exact equilibration level is determined by the dialysate Ca2+ concentration, not by its total calcium concentration.

In summary, we conclude that measurement of pCa2+ and PTH before and after HD appears to be a promising tool to monitor calcium balance in individual patients. It may help to fine-tune the choice of a patient-specific, optimal dialysate calcium concentration. The changes in pCa2+ and PTH of samples obtained at the end of a previous session and at the beginning of the next HD session reflect calcium balance between dialyses, and these data should provide information to adjust the oral intake of calcium, vitamin D, phosphate binders and calcimimetics. In steady state conditions, and with appropriate control of serum phosphate, magnesium and bicarbonate levels, the combination of a low pCa2+ and elevated PTH suggests a negative calcium balance, either caused by HD or by conditions between di-
alysis sessions. A decline in pCa\textsuperscript{2+} with a concomitant rise in PTH during HD suggests dialysis-induced calcium loss and may require an adjustment of dialysate calcium concentration. A decreasing pCa\textsuperscript{2+} and increasing PTH between HD sessions suggests a negative calcium balance between dialyses and should prompt actions to improve calcium intake and/or to optimize vitamin D status. It is well recognized that these expectations do need further validation.

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REFERENCES