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Research Article

Personalized Monitoring of Calcium Flux Direction during Haemodialysis

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Abstract

Background: Personalized monitoring of calcium flux direction during hemodialysis HD may help to avoid the adverse effects of calcium depletion or calcium excess.

Aim: To evaluate whether pre- and post-HD measurement of plasma ionized calcium pCa^{2+} and parathyroid hormone PTH provides useful information on calcium flux direction during HD in individual patients.

Methods: Observational, single centre study in 86 patients on a dialysate calcium DCa of 1.25 mmol/L or 1.50 mmol/L. Main outcome measure: the percentage of patients with physiologically sound combinations of pCa^{2+} and PTH responses, i.e. a decline in pCa^{2+} associated with an increase in PTH, or a rise in pCa^{2+} associated with a decline in PTH.

Results: Physiologically sound combinations of pCa^{2+} and PTH responses were observed in 85% of patients. If limited to patients demonstrating HD induced changes in pCa^{2+} > 0.1 mmol/L and/or changes in PTH > 10 pmol/L, concordant responses were observed in 98% of cases.

Conclusion: The high degree of physiologically sound combinations of pCa^{2+} and PTH suggests that pCa^{2+}/PTH monitoring has potential as an instrument to guide calcium flux management during HD, and may help to assess the optimal DCa on a personal basis. It remains to be shown whether this approach can decrease the prevalence of complications related to calcium depletion or calcium excess.

INTRODUCTION

Adverse effects related to calcium depletion and calcium excess is and will remain common in patients on hemodialysis HD as long as practical and validated tools to monitor calcium redistribution during HD are not available. Maintaining zero calcium mass balance Ca_{MB} is generally believed to prevent calcium related complications [1]. However, Ca_{MB} management is extremely complex and its assessment represents a major challenge because of the many variables that are involved [2,3]. Food calcium content, fractional calcium absorption, type of phosphate binders, vitamin D status and calcium exchange during HD will all affect calcium balance [2,4]. An exact quantification of all these effects on a personal level is virtually impossible to achieve, and with current methods it is not feasible in daily practice. We hypothesize that such a detailed approach may not be necessary and propose to explore a more simple method that is focused on assessment of calcium flux direction instead of an exact quantification of Ca_{MB} in mass units. As calcium exchange during HD is a major factor of overall Ca_{MB}, knowledge of calcium flux direction and a qualitative estimate of the degree of calcium exchange during HD may contribute to improve treatment. Knowing whether there is calcium influx or efflux during HD, and an indication whether the exchange is large or small may provide the guidance needed to choose the most appropriate dialysate calcium concentration DCa in individual patients.

The degree of damage done by calcium in- or efflux during HD will depend on the pattern of internal calcium redistribution. Calcium exchange during HD is primarily driven by the dialysate-plasma DP calcium gradient. If there is a gradient, it will induce calcium exchange over four compartments in a fixed sequence: a positive DP gradient will induce a calcium flux from the dialysate into the blood, into the interstitial fluid and then into the bone exchangeable calcium pool BECP, whereas a negative gradient

will cause a calcium efflux from the blood into the dialysate with replenishment of the blood calcium compartment from the interstitial fluid and the BECP [5]. The BECP is as a fast-acting buffer that counteracts and mitigates the changes in plasma ionized calcium pCa^{2+} induced by HD. If its buffer capacity is exceeded by a massive calcium influx from the dialysate into the blood there is a high risk of hypercalcemia and soft tissue calcification. On the other hand, if the calcium efflux from the blood into the dialysate is greater than the replenishment capacity of the BECP, adverse effects related to hypocalcemia will occur. Plasma Ca^{2+} change during HD can be regarded as a key indicator of the BECP's capacity to store or donate calcium: pCa^{2+} will rise if the BECP storage capacity is exceeded, it will decrease if the capacity to mobilize calcium has reached its maximum. These HD induced changes in pCa^{2+} will be detected by the parathyroid calcium sensing CaS receptor, and this will elicit a PTH response that activates mechanisms counteracting the HD induced changes in pCa^{2+} in the mid- and long term [6]. We hypothesize that monitoring of this feedback loop, by way of measuring pCa^{2+} and PTH at the beginning and end of HD may serve as a warning device that produces reliable signals if the buffering capacity of the BECP is overwhelmed, and there is a risk of tissue calcification or of calcium loss.

Several investigational steps will be needed to examine the potential clinical value of this approach. As it is based on the premise that the pCa^{2+}/PTH negative feedback loop is intact, the first step will be to assess whether repeated measurement of pCa^{2+} and PTH at the beginning and end of HD is sufficiently sensitive and accurate to generate physiologically sound information. Since changes in pCa^{2+} are detected by the parathyroid CaS receptor and elicit reciprocal changes in PTH, only two types of combinations can be valid: a decline in pCa^{2+} associated with a rise in PTH, and a rise in pCa^{2+} associated with a decline in PTH [7, 8]. To date, several studies have shown that, on a group level, these pCa^{2+}/PTH response combinations produce the same information on calcium flux direction as classical mass balance assessments [9-15]. However, performance quality on an individual level is currently not known. The aim of the present study was to assess the percentage of physiologically sound pCa^{2+}/PTH combinations in patients on HD in a general hospital dialysis unit.

PATIENTS AND METHODS

This is an observational, cross-sectional, single centre study of patients on daytime HD three times a week, on stable dialysate calcium concentration DCa and stable medication for at least 4 weeks. Patients who had undergone total parathyroidectomy and those who were treated with cinacalcet were excluded. HD was performed with a cellulose triacetate filter. Patients were either treated with a DCa of 1.25 mmol/L 1.25DCa or 1.50 mmol/L 1.50DCa. Blood samples were taken from the blood inlet line, just before the filter, at the beginning and the end of a 4-hour HD session during 4 consecutive sessions. Dietary calcium intake was estimated by questionnaire. The study was performed according to the regulations of the hospital's ethics committee, and all included patients gave their informed consent prior to the start of the study.

Laboratory assays

Plasma total calcium, phosphate, magnesium, and albumin were measured with standard laboratory assays Modular Analytics P800, Roche Diagnostics, Mannheim, Germany. Plasma bicarbonate, Ca^{2+}, base excess, and pH were measured by blood gas analyzer using ion-selective electrodes OMNI Roche, Mannheim, Germany. Serum intact PTH normal range: 1.3 – 6.8 pmol/L was measured by a solid-phase, two-site chemoluminiscent enzyme-labeled immunometric assay DPC, Los Angeles, USA, with intra- and interassay coefficients of variation of < 6% and < 9%, respectively. 25-OH vitamin D 25OHD was measured by direct competitive chemiluminescence immunoassay Diasorin Inc., Stillwater, USA. Serum 1.25-OH_2 vitamin D 1.25OHD was measured by radioimmunoassay Immunodiagnostic Systems GmbH, Frankfurt am Main, Germany. The bone markers PINP bone formation and ICTP bone resorption were both measured by immunoradiometric assay Orion Diagnostica, Espoo, Finland: PINP intra- and interassay precision of 7.8% and 8.3%, intra- and interassay precision 6.4% and 7.3%, respectively. Normal ranges are: pCa^{2+} 1.10 - 1.33 mmol/L interassay coefficient of variation 2.2% , 25OHD 50 - 125 nmol/L, 1.25OHD 75 - 150 pmol/L, PINP 22.0 - 87.0 ug/L, ICTP 2.1 - 5.0 ug/L. According to KDIGO 2009, PTH levels in patients on HD should be maintained between 2 – 9 times the assays upper normal limit. Therefore, in this study PTH's lower normal limit LNL_{KDIGO} was set at 13.6 pmol/L, and its upper normal limit UNL_{KDIGO} at 61.2 pmol/L.

Statistics

Results are shown as mean values ± standard error of the mean SE. Pre- and post-HD data with normal distribution were compared by paired student t-test, and by Wilcoxon signed rank test if the data were not normally distributed. Correlations between data were studied by linear or polynomial regression analysis. A P-value < 0.05 was considered statistically significant.

RESULTS

General patient characteristics

Eighty-six out of 90 patients meeting the inclusion criteria agreed to participate in the study and signed an informed consent. Seventy patients were treated with 1.25DCa, and 16 with 1.50DCa. Mean pCa^{2+} and PTH levels measured at the start of HD p_0Ca^{2+} and PTH_0, respectively were 1.16 ± 0.01 mmol/L range 0.95 – 1.40 mmol/L, and 32.5 2.6 pmol/L range 4.6 – 125.7 pmol/L. Individual values are shown in figure 1, demonstrating wide ranges in p_0Ca^{2+} and PTH_0 levels: 18/86 21% of patients had p_0Ca^{2+} levels < 1.10 mmol/L and 23/86 27% had PTH_0 levels outside the range recommended by KDIGO 2009: 16 patients had PTH levels below the LNL_{KDIGO}, and 7 patients had PTH levels exceeding the UNL_{KDIGO}. Thirteen patients 15% received cholecalciferol 50.000 IU/month, and 87% of patients were treated with 1α-calcidiol, with doses ranging from 0.11-1.70 μg/day. Twenty-nine patients 34% received calcium supplements. Seventy-seven patients 90% used phosphate binders, either sevelamer N = 75, fosrenol N = 19 and/or algeldrate N = 2. Vitamin D deficiency, defined as a 25OHD level < 50 nmol//L, was found in 78% of patients, and suboptimal 1.25OHD levels, defined as a 1.25OHD < 75 pmol/L, were found in 95% of patients. Of note, 1.25OHD deficiency was found in 62 out of 63 patients 98% despite of PTH levels within the KDIGO limits.

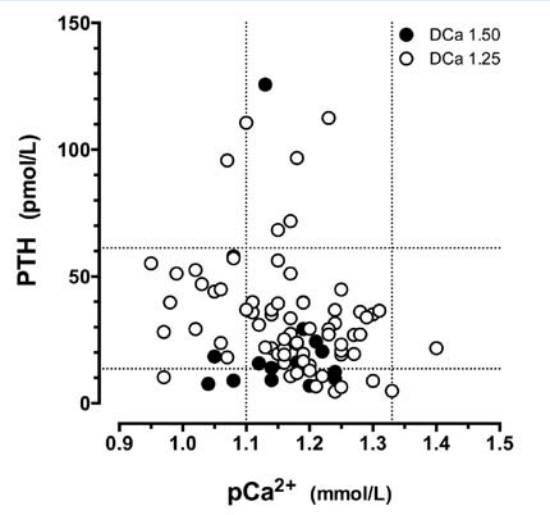

Figure 1 Ranges of plasma ionized calcium pCa2+ and PTH levels in 86 patients, measured at the start of hemodialysis. The vertical dotted lines represent the pCa2+ normal range. The KDIGO 2009 recommended PTH limits are shown as horizontal dotted lines. Open circle, dialysate calcium 1.25 mmol/L; black dot, dialysate calcium 1.50 mmol/L.

Calcium and PTH changes induced by HD

The relationship between HD-induced changes in pCa^{2+} ΔpCa^{2+} and changes in PTH ΔPTH is shown in figure 2. It contains the data of patients on 1.25DCa open circles as well as of those on 1.50DCa black dots. As expected, changes in pCa^{2+} were inversely correlated with changes in PTH levels R= -0.60, P < 0.001. This relationship is described by a line with a slope of - 90 95% CI: -117 to -64 and an intercept of +0.84 95% CI: -1.6 to 3.3. Based on these 95% confidence intervals of slope and intercept the equation can be simplified into: $\Delta PTH = - 100 \times \Delta pCa^{2+}$. In other words, PTH changed by approximately 10 pmol/L for every 0.1 mmol/L change in pCa^{2+}.

Assessment of calcium and PTH responses in individual patients

Results of pCa^{2+} and PTH measurements were concordant in 73 patients 85%, i.e. they either demonstrated a decrease in pCa^{2+} that was associated with an increase in PTH or they had an increase in pCa^{2+} associated with a decrease in PTH (figure 2): all patients in sections A and D. In this group with concordant responses, the changes in pCa^{2+} were inversely correlated with the changes in PTH R = -0.66, P < 0.001. However, inter-individual variation in PTH responses was considerable (figure 3).

Results of pCa^{2+} and PTH measurements were discordant in 13 patients 15%, (figure 2): all patients in sections B and C. Six demonstrated a simultaneous decrease in pCa^{2+} and PTH, and 7 patients had a simultaneous increase of both parameters. However, the majority of these discordant responses occurred when changes in pCa^{2+} or PTH were small. When assessment of concordance rates was limited to patients with abnormal baseline pCa^{2+} or PTH levels, i.e. those who either had a p_0Ca^{2+} < 1.10 mmol/L and/or a PTH_0 outside the KDIGO recommended range, the concordance rate was 30/37 =81%. Alternatively, if only changes in pCa^{2+} > 0.1 mmol/L and/or changes in PTH > 10 pmol/L are considered as clinically relevant, 42/86 49% patients met these criteria, with a concordant response in 41 cases 98%.

Effects of dialysate calcium concentration

Seventy patients were treated with 1.25DCa and 16 were on 1.50DCa. General baseline characteristics of the two groups are summarized in table 1. Despite comparable p_0Ca^{2+} levels, PTH_0 levels were markedly higher in patients on 1.25DCa than in those on 1.50DCa 34.5 ± 2.7 pmol/L versus 23.9 ± 7.1 pmol/L, P < 0.01. Patients on 1.25DCa also tended to have a higher dietary calcium intake and used additional calcium supplements more frequently and in higher doses than patients on 1.50DCa. In addition, patients on 1.25DCa used cholecalciferol, 1α-calcidiol, and phosphate binders more frequently and in higher doses than patients on 1.50DCa (Table 2).

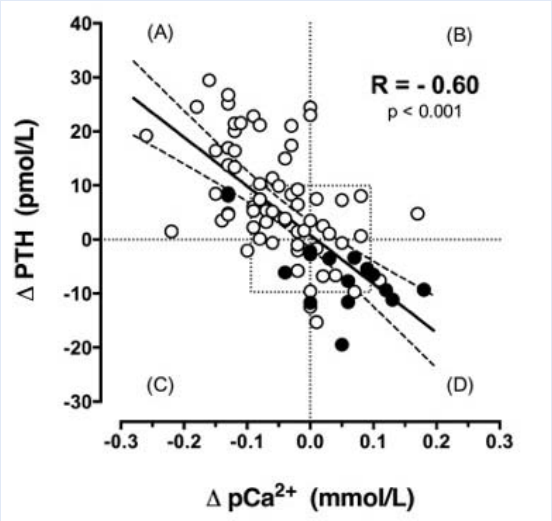

Figure 2 Changes in plasma PTH Δ PTH in relation to changes in plasma ionized calcium Δ pCa2+ during hemodialysis in 86 patients on dialysates with 1.25 or 1.50 mmol calcium per liter N=86. Open dot: 1.25DCa. Black dots: 1.50DCa.

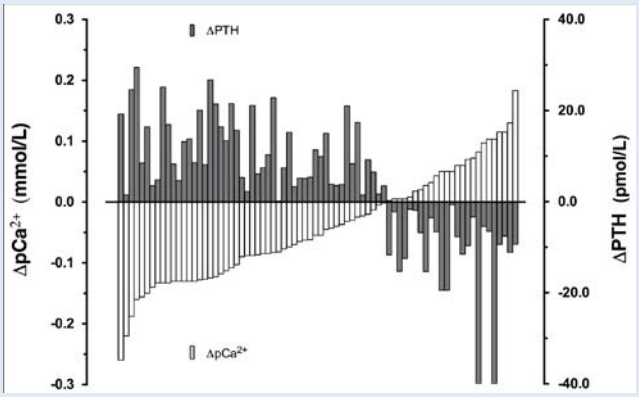

Figure 3 All 73 patients with concordant pCa^{2+}/PTH responses, arranged according to the magnitude of change in pCa^{2+}. White bars: change in pCa^{2+}, gray bars: change in PTH.

As expected, patients on 1.25DCa responded differently than those on 1.50DCa (Table 3). 1.25DCa induced a decrease in pCa^{2+} from 1.17 ± 0.01 mmol/L to 1.11 ± 0.01 mmol/L P < 0.001 with a concomitant increase in PTH from 34.5 ± 2.7 pmol/L to 41.6 ± 3.0 pmol/L P < 0.001, whereas 1.50DCa caused an increase in pCa^{2+} from 1.16 ± 0.02 mmol/L to 1.21 ± 0.01 mmol/L P <0.001, and a decrease in PTH from 23.9 ± 7.1 pmol/L to 13.8 ± 3.8 pmol/L P < 0.001. Although both dialysate groups had similar pCa^{2+} levels at the start of HD, at the end of HD pCa^{2+} was 10% lower in patients on 1.25DCa than in those on 1.50DCa P < 0.01. At the start of HD, PTH levels were 45% higher in patients on 1.25DCa than in patients on 1.50DCA, and this difference increased to 200% at the end of HD.

Effects of PO4 and $Mg2^{+}$on PTH levels

To address the question whether PTH levels were affected by HD-induced changes in PO_4 and Mg^{2+}, independent of the change in pCa^{2+} ΔpCa^{2+}, we selected all patients who had a ΔpCa^{2+} < 2% to eliminate the effect of pCa^{2+} on PTH secretion. In this subgroup without significant changes in pCa^{2+} N=20, PTH did not change, despite significant changes in phosphate, magnesium and bicarbonate data not shown. In addition, in a multiple regression analysis model, ΔPTH was only related to ΔpCa^{2+} R = -0.60, p < 0.001.

Table 1: Baseline characteristics and plasma Ca^{2+}, PO4 and PTH levels measured at the start of haemodialysis in patients treated with a dialysate calcium concentration of 1.25 or 1.50 mmol/L, respectively.

	1.25 DCa N= 70	**1.50 DCa** N= 16
Sex male/female	47/23	10/6
Age years	67.1±1.7	68.7 ± 3.3
Weight kg	76.2±2.0	75.1 ± 3.2
pCa^{2+} mmol/L	1.17 ± 0.01	1.16 ± 0.02
PO4 mmol/L	1.73 ± 0.06	1.44 ± 0.15
PTH pmol/L	34.5 ± 2.7[1]	23.9 ± 7.1
25OHD nmol/L	36.7 ± 2.9	31.9 ± 4.5
25OHD < 50 nmol/L	74%	94%
1.25OHD pmol/L	42.2 ± 2.5	40.4 ± 4.1
1.25OHD < 75 pmol/L	96%	94%
ICTP g/L	93 ± 7	66 ± 8
PINP.. µg/L	42 ± 3	58 ± 18

[1], P < 0.01

Table 2: Comparison of dietary calcium intake and medications affecting calcium and/or phosphate balance in patients treated with dialysate calcium concentrations of 1.25 and 1.50 mmol/L. Figures expressed in percentages reflect the percentage of patients using the specified medication.

	1.25 DCa N=70	**1.50 DCa** N=16	**P** *
Dietary Calcium intake mg/day	743±53	463±111	0.45
Calcium supplements mg/day	1640±640 36%	1188±344 25%	0.99 0.32
Cholecalciferol IU/month	57692±5208 19%	0 0%	 0.17
1α-calcidiol µg/day	0.64±0.04 90%	0.38±0.05 75%	0.03 0.24
Sevelamer mg/day	5338±271 91%	3855±480 69%	0.02 0.23
Fosrenol mg/day	2083±177 26%	750±0 6%	0.99 0.32
Algeldrate mg/day	1750±250 3%	 0%	 0.79

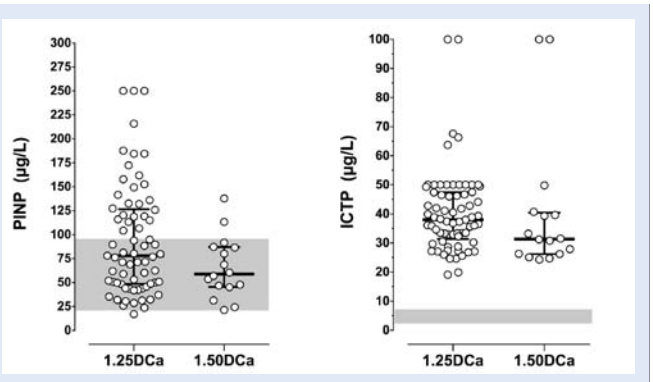

Figure 4 Bone turnover as assessed by the serum bone formation marker PINP and the bone resorption marker ICTP. The gray areas represent the normal range in healthy subjects.

Bone turnover

Bone turnover assessed by measurement of serum ICTP marker of bone resorption and PINP marker of bone formation indicated high bone turnover in the majority of patients. All patients had ICTP levels exceeding the upper normal limit, and 98% had PINP levels within or above the upper normal limit (Figure 4). Only 2 patients had PINP levels just below the lower normal limit.

Minimal sample number required for analysis

The present analysis was based on the average of 4 measurements for each time point. Re-analyses with data based on 3, 2 or 1 consecutive HD sessions showed that the concordance rates of pCa^{2+}/PTH changes decreased from 85% to 80%, 81% and 77% respectively. Decreasing the number of samples also affected the observed direction of change in pCa^{2+} and/or PTH. For 3, 2 and 1 sample analyses, the direction of change of pCa^{2+} reverted into the opposite direction in 0, 4 and 7 patients respectively, and for PTH this occurred in 3, 4 and 14 patients respectively.

DISCUSSION

The present study should be regarded as a preliminary evaluation of the potential value of individualized calcium flux monitoring during HD, by way of measuring pCa^{2+} and PTH at the start and end of HD. We assessed the applicability of this method in an unselected group of patients in a general hospital dialysis unit, using the number of physiologically sound, i.e. concordant, combinations of pCa^{2+}/PTH measurements as outcome measure. The overall concordance rate of pCa^{2+}/PTH measurements was 85%, and 81% if testing was limited to patients with pCa^{2+} < 1.10 mmol/L and /or PTH levels outside the KDIGO recommended limits at the start of HD. The concordance rate increased to 98% if limited to patients with HD-induced changes in pCa^{2+} > 0.1 mmol/L and/or changes in PTH > 10 pmol/L. Although arbitrary,

Table 3: Hemodialysis induced changes in patients on 1.25DCa N = 70 or on 1.50DCa N = 16.

		Pre-Dialysis	Post-dialysis	P*
Ca^{2+} mmol/L	1.25DCa	1.17±0.01	1.11±0.01	< 0.001
	1.50DCa	1.16±0.02	1.21±0.01[1]	0.03
PO4 mmol/L	1.25DCa	1.73±0.06	0.75±0.02	< 0.001
	1.50DCa	1.44±0.15	0.65±0.03[2]	0.001
Mg^{2+} mmol/L	1.25DCa	1.00±0.08	0.89±0.11	< 0.001
	1.50DCa	0.87±0.03	0.76±0.01	< 0.001
HCO_3^- mmol/L	1.25DCa	22.6±0.3	28.1±0.2	< 0.001
	1.50DCa	22.2±0.6	27.7±0.4	< 0.001
PTH pmol/L	1.25DCa	34.5±2.7	41.6±3.0	< 0.001
	1.50DCa	23.9±7.1[1]	13.8±3.8[1]	0.002

P*, comparison of changes within groups
[1], P < 0.01; [2], P < 0.05 for the comparison between groups

Table 4: Comparison of intradialytic calcium flux direction based on calcium mass balance Ca_{MB} assessment and measurement of plasma calcium/PTH changes during hemodialysis. Note, all reported changes in Ca_{MB}, ΔpCa, or ΔPTH are statistically significant P < 0.05, unless marked with asterix *

DCa mmol/L	Reference	N	p_0Ca	Ca_{MB} mmol	ΔpCa %	ΔPTH %	Discrepancy
0.75	Hou[12]	7	2.27[a]	-5.8 ± 1.0	-9.7	ND	No
1.25	Hou[12]	7	2.27[a]	+5.4 ± 3.4*	+2.2*	ND	No
	Bosticardo[13]	22	1.15	-1.4 ± 0.4	-0.7*	ND	Yes
	Fabrizi[2]	6	1.20[b]	-0.14 ± 0.4*	-0.8*	-1.4*	No
	Basile[8]	22	1.24[b]	+1.9 ± 0.7	-3.2	+47	Yes
1.38	Basile[8]	22	1.25	+4.6 ± 0.7	+2.4	-12	No
1.50	Bosticardo[13]	22	1.16	+2.3 ± 0.6	+7.0	ND	No
	Basile[8]	22	1.26	+7.4 ± 1.2	+5.5	-17	No
1.75	Hou[12]	7	2.25[a]	+21.9 ± 2.3	+12.0	ND	No
	Fabrizi[2]	6	1.21[b]	+7.7 ± 0.6	+19.8	-66.3	No

DCa = dialysate calcium concentration mmol/L, Ref = reference number, N = number of patients, p_0Ca = plasma total or ionized calcium measured at the start of HD from the blood inlet line, Ca_{MB} = calcium mass balance in mmol, mean ± SE, ΔCa = % change in total or ionized calcium during HD, ΔPTH = % change in PTH levels during HD, ND=not done
[a] = total calcium, [b] = Ca^{2+},* = not significant, all other changes are at least P < 0.05,

these latter cut-offs were chosen because changes of these magnitudes are well outside the range of assay inaccuracies, and thus likely to reflect physiological meaningful changes. Adjustment of treatment may be needed in these patients, and we hypothesize that the provided knowledge of calcium flux direction may be helpful to guide these adjustments. However, several issues will need further clarification and validation before introduction in clinical practice can be considered.

First, although pCa^{2+} is the most important feedback for PTH secretion, PTH levels may also change in response to changes in plasma phosphate, magnesium and pH [7, 16-19]. To investigate the impact of these secondary factors, a sub-analysis was performed in patients who had a change in pCa^{2+} < 2%. This showed that PTH levels remained stable during HD despite marked changes in phosphate, Mg and bicarbonate. Moreover, in a multiple regression analysis including all 86 patients, ΔpCa^{2+} emerged as the only variable affecting PTH changes. We therefore conclude that the PTH response during HD is mainly determined by changes in pCa^{2+}, and that the impact of other variables is negligible in a normal clinical situation. This conclusion is also supported by the relationship between ΔpCa^{2+} and ΔPTH, illustrated in figure 2. It shows that the regression line runs exactly through the zero point, which is additional evidence that this line describes a physiological meaningful relationship: if there is no change in pCa^{2+} there is also no change in PTH, and if there is a decrease in pCa^{2+} there is an increase in PTH, and vice versa.

Secondly, although the changes in pCa^{2+} and PTH were well correlated, it is also obvious that inter-individual variation in PTH responses was substantial [Figure 3]. Part of this variability may be assay-related, but physiological factors may also play a role. The magnitude of the PTH response may not only depend on the magnitude of ΔpCa^{2+}, but also on the parathyroid's calcium sensor's sensitivity, its set point, and the pCa^{2+} level at the start of HD. Parathyroid calcium sensor's with a narrowly set normal range are likely to respond with larger PTH excursions than sensors with a widely set normal range [20].

The concept is that pCa^{2+}/PTH measurements can be used as a tool to assess calcium flux direction between the blood and dialysate because the DP gradient is the main factor inducing changes in pCa^{2+} and PTH. During HD, the BECP is not a primary driving force, it acts as a reactive system [5]. Calcium fluxes from and to the BECP occur in response to, i.e. secondary to changes in pCa^{2+}. In the present patient population where the majority

was treated with 1.25DCa bone turnover assessed by serum ICTP and PINP was very high. This is attributed to secondary hyperparathyroidism as a result of HD-induced calcium loss that occurred in the majority of patients. Raising the DCa is likely to benefit these patients.

The reliability of pCa^{2+}/PTH measurement as marker of calcium flux direction can be deduced from studies that combined classical Ca_{MB} techniques with measurements of pre- and post-dialysis measurement of pCa^{2+} and PTH. Most of these studies have confirmed that both approaches produce identical results on calcium flux direction [9-15, 21]. In all studies on HDF, calcium flux directions based on pCa^{2+}/PTH measurements were similar to those obtained by Ca_{MB} on a group level [11-13]. In patients on HD, and treated with DCa < 1.25 mmol/L or > 1.25 mmol/L, both methods also produced identical results table 4. However, conflicting results emerged when a DCa of 1.25 mmol/L was studied [9, 10, 14, 15]. Two studies reported concordant results [9,14], whereas two other studies reported conflicting data [10,15] (Table 4). In Bosticardo's study the net loss of 1.4 mmol calcium per session was not associated with a statistically significant decline in pCa^{2+} [12]. In Basile's study, the decline in pCa^{2+} with a concordant increase in PTH was in conflict with the finding of a 1.9-mmol positive calcium balance per session [5]. The conflicting mass balance results of the four studies evaluating 1.25DCa, and Basile's intrinsic paradoxical findings are difficult to explain and suggest an error of measurement (Table 4). Most arguments indicate that mass balance results are too insensitive for accurate detection of flux direction when DP gradients are small. Although the classical balance method is generally regarded as the golden standard, there are no data to justify that. To our knowledge, its degree of accuracy has never been assessed, and we believe that the errors involved in handling large volumes, in measuring Ca^{2+} concentrations in protein-rich and protein-poor fluids, and of assumptions in calculation procedures are not likely to be negligible.

It is important to note that pCa^{2+}/PTH measurements can only serve as a warning device to detect major calcium fluxes between the blood and the dialysate. They are not an exact substitute for total mass balance. As long as the BECP is capable of rapidly correcting the HD-induced changes in pCa^{2+}, the changes in pCa^{2+} will be small and remain within the assay's error margins, and net transfer of calcium from the dialysate to the BECP or vice versa will go undetected. Probably, these minor exchanges are harmless. However, major calcium fluxes that exceed the buffering capacity of the BECP will be detectable, and they are likely to be clinically important.

Current evidence is insufficient to conclude that HD-induced changes in pCa^{2+} and PTH are clinically useful to predict calcium flux direction without further validation against a golden standard. As discussed, classical mass balance methods are unlikely to be sufficiently accurate to serve as golden standard when used on an individual level. Therefore, alternative validation procedures need to be developed [15]. Sensitive methods to quantify bone calcium mobilisation and soft-tissue calcification would be most helpful to further validate the flux direction concept. Alternatively, the concept might be tested by evaluation of long-term outcome in a prospective study.

Measurement of pCa^{2+} and PTH before and after HD during 4 consecutive HD's is expensive. Reduction of the number of measurements would be most welcome if it does not affect the reliability of observations. Sample reduction to three sessions does not affect the interpretation. Limited discrepancies appear if samples are only taken during 2 sessions. For the present we recommend using the datasets of 3 consecutive HD sessions.

In conclusion, measurement of pre-and post-HD pCa^{2+} and PTH appears to be a sensitive tool to assess the HD-induced calcium flux direction in individual patients. It remains to be shown whether treatment guidance based on these measurements can help to reduce the prevalence of complications induced by calcium depletion or excess.

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