Antihypertensive Effect of Low Calcium Dialysis

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Abstract

Background: During maintenance hemodialysis acute elevation in serum calcium is common. Low calcium dialysis is advocated as a therapy for prevention of dialysis-induced hypercalcemia. Approximately 16% of our chronic hemodialysis patients experience elevated arterial blood pressure during the hemodialysis session, becoming hypertensive by the end of the treatment. All these patients exhibited post-dialysis hypercalcemia.

Objectives: To investigate the effect of low calcium dialysis on post-dialysis hypertension in view of an evident link between serum calcium and blood pressure in both normal renal function and chronic renal failure patients.

Methods: We evaluated 19 chronic hemodialysis patients in whom both post-dialysis hypertension and PDHCa were observed. We investigated changes in serum total calcium, ionized calcium, intact parathormone levels and arterial blood pressure in response to 4 weeks low calcium dialysis as a treatment for PDHCa.

Results: When PDHT patients were treated with low calcium dialysis, post-dialysis blood pressure was significantly decreased compared to pre-dialysis values (155.3 ± 9.7/82.2 ± 7.9 mmHg pre-dialysis vs. 134.1 ± 20.8/80 ± 8.6 mmHg post-dialysis, P = 0.001). Additionally, post-dialysis blood pressure was significantly lower than post-dialysis blood pressure prior to the low calcium dialysis treatment (176.1 ± 15/86 ± 10.8 mmHg post-standard dialysis, 134.1 ± 20.8/80 ± 8.6 mmHg after low calcium dialysis, P = 0.001). A decline in post-dialysis serum calcium (2.34 ± 0.2 vs. 2.86 ± 0.12 mmol/L, P = 0.04) and ionized calcium (1.17 ± 0.12 vs. 1.3 ± 0.06 mmol/L, P = 0.03) compared to pre-dialysis levels was also achieved by this treatment, with no significant changes in iPTH levels.

Conclusions: These data suggest a role for low calcium dialysis in treating acute serum calcium elevation and post-dialysis hypertension in patients receiving maintenance hemodialysis.

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The association between high serum calcium level and elevated systemic blood pressure is well established [1–4], especially in patients with progressive renal failure. Similarly, a sharp decline in blood pressure as a result of acute hypocalcemia has also been described, including in patients after parathyroidectomy [3–5]. Several mechanisms for the association between calcium and hypertension have been postulated, such as intensification of contractile capability of the vascular smooth muscles and the myocardium by direct effect of ionized calcium [1,3], and up-regulation of the renin-angiotensin-aldosterone system and catecholamine release due to calcium load [6–8]. Although the most common unfavorable hemodynamic change during maintenance hemodialysis is hypotension, a significant number of dialysis patients develop an elevation of blood pressure during hemodialysis that persists for several hours after the end of the dialysis session. There is no widely accepted explanation for this phenomenon, which is considered a risk factor for life-threatening cardio- and cerebrovascular events [9].

Acute elevation of serum calcium concentration is not unusual during maintenance hemodialysis in patients with chronic renal failure [10]. This transient hypercalcemia, which gradually returns to normal within several hours, may reflect: a) diffusion of calcium from dialysate to blood, b) increased plasma protein calcium binding due to either increased plasma pH or the removal of an inhibitor to protein binding of calcium, c) acute dialysis phosphate and magnesium loss causing shifting of intracellular calcium to the plasma, and d) increased concentration of protein-bound calcium following ultrafiltration and subsequent hemoconcentration. The long-term clinical consequences of post-dialysis hypercalcemia are not well established. Carney and Gillies [11] contended that it plays a role in the formation of renal osteodystrophy by causing the removal of phosphorus from bone. It is advised to use lower dialysate calcium concentration to prevent or treat hypercalcemia [10].

Presented here is a case series in which the effect of low calcium dialysis on hemodialysis patients with both PDHCa and post-dialysis hypertension was examined.

Patients and Methods

All maintenance hemodialysis patients treated at our facility (n=127) were screened for post-dialysis arterial hypertension. PDHT was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 [12], recorded at the end of each dialysis session during a 4 week period. Nineteen PDHT patients were identified, all of whom had PDHCa on regular dialysate and were well dialyzed (Kt/V > 1.2) and euvolemic, with no requirement for fluid infusion during dialysis sessions. None of them had hypoalbuminemia (serum albumin ≥3.8 g/dl).

Patients were characterized in terms of age, gender, years of dialysis treatment, and need for antihypertensive drugs (amount and type). After baseline, PDHT patients were switched from their usual dialysate (high calcium) containing 1.5 mmol/L calcium (Teva Medical, Ashdod, Israel) to a low calcium dialysis regimen (1.25 mmol/L calcium, Teva) as the sole change in dialysate composition. The use of a concentrate of low calcium

PDHCa = post-dialysis hypercalcemia
PDHT = post-dialysis hypertension
iPTH = intact parathormone

dialysate, which is available and provided by the above-mentioned manufacturer, constituted the change. No other treatment changes were made, not in the dialysis program, medications or nutritional instructions. Blood pressure measurements were recorded in the sitting position, using a model 9300 NIBP electronic monitor (CAS Medical Systems, Branford, USA). Blood pressure was recorded before and at the end of each dialysis session at baseline and during the 4 week period in which patients received low calcium dialysis.

Serum intact parathormone levels (using Nichol's method), total calcium and ionized calcium pre- and post-dialysis session were examined, each time in the same blood sample: one at baseline and again after the 4 week low calcium dialysis intervention. All blood tests were performed according to the standard protocol of the Biochemistry Laboratory at Wolfson Medical Center. Ionized calcium measurements were performed with the Gem Premier 3000 Model 5700 (Instrumentation Laboratory, Lexington, MA, USA). The normal range was 1.18–1.29 mmol/L.

Data analysis

Data were stored on Excel 97 with Hebrew Language support (Microsoft Inc., Seattle, WA, USA 1985-1997). Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc., Chicago, USA, 1999). For continuous variables such as age, blood pressure and serum calcium, descriptive statistics were calculated and are reported as mean ± standard deviation. The distributions of these variables were tested for normalcy, using the Kolmogosov-Smirnov test. Means of normally distributed variables (e.g., age, blood pressure) were compared by PDHT status using the *t*-test for independent samples. Means of variables with highly skewed distributions (e.g., serum ionized calcium, PTH) were compared between PDHT patients and controls using the Mann-Whitney U test. Comparisons of continuous variables pre- and post-low calcium intervention in PDHT patients was carried out using the *t*-test for paired samples or the Wilcoxon Signed Rank Test. Categorical variables such as gender and medications were described using frequency distributions. Chi-square (with Yates correction as needed) was used to detect differences in categorical variables by PDHT status and also in PDHT patients by pre- and post-intervention status. All tests were considered significant at $P < 0.05$.

Results

The characteristics of PDHT patients at baseline are presented in Table 1. Compared with all other patients in the dialysis unit, PDHT patients were older (68.5 ± 12.5 vs. 60.4 ± 13.8 years, $P = 0.04$) and had significantly elevated post-dialysis systolic (176.1 ± 15 vs. 130.5 ± 21.7 mmHg, $P = 0.0001$) and diastolic (86 ± 10.8 vs. 75.3 ± 10.2 mmHg, $P = 0.008$) blood pressure. Differences in pre-dialysis blood pressure were not detected. Similarly, a greater percentage of PDHT patients received antihypertensive therapy than did other hemodialysis patients (47.4% vs. 36.8%, $P = 0.01$).

In PDHT patients, the 4 week intervention with low calcium dialysis was associated with a significant reduction in mean post-dialysis serum total calcium (2.34 ± 0.2 vs. 2.86 ± 0.12 mmol/L, $P = 0.04$, Figure 1), as well as serum ionized calcium (1.17 ± 0.12 vs. 1.3 ± 0.06 mmol/L, $P = 0.03$, Figure 2) compared to baseline. Serum levels of iPTH were not influenced by low calcium dialysis (290.8 ± 84.4 post-dialysis vs. 286.3 ± 73.1 pg/ml pre-dialysis, $P = 0.01$). High calcium (baseline) pre-dialysis blood pressure in PDHT patients (157.9 ± 15.4/80.8 ± 8.6 mmHg) did not significantly differ from pre-dialysis measurements after 4 weeks of low calcium dialysis (155.3 ± 9.7/82 ± 7.9 mmHg). On the other hand, baseline post-dialysis blood pressure was significantly higher than post-dialysis blood pressure after the 4 week low calcium intervention (176 ± 15/86 ± 10.8 vs.134.1 ± 20.8/80 ± 8.6 mmHg, $P = 0.001$, Figure 3). There were no significant changes in PDHT patients' mean body weight decrease during dialysis after the whole period of low calcium dialysis treatment related to high calcium dialysis treatment: 2.41 ± 0.19 kg (high calcium) vs. 2.27 ± 0.23 kg (low calcium), $P = 0.104$.

Table 1. Characteristics and baseline data of patients with and without PDHT, on high calcium hemodialysis

	PDHT group (n=19)	Hemodialysis patients without PDHT (n=108)	*P*
Age (yrs)	68.5 ± 12.5	60.4 ± 13.8	0.04
Females (%)	21.1	36.8	NS
Hemodialysis (yrs)	3.6 ± 5.4	5.16 ± 5.6	NS
Serum iPTH (pg/ml)			
Pre-dialysis	299.7 ± 77.4	300.6 ± 264.6	NS
Post-dialysis	304.3 ± 86.1	296.1 ± 270.6	NS
Serum Ca (mmol/L)			
Pre-dialysis	2.36 ± 0.15	2.38 ± 0.12	NS
Post-dialysis	2.86 ± 0.12	2.83 ± 0.14	NS
Serum ionized Ca (mmol/L)			
Pre-dialysis	1.2 ± 0.1	1.2 ± 0.1	NS
Post-dialysis	1.3 ± 0.06	1.4 ± 0.09	NS
Blood pressure (mmHg)			
Pre-dialysis			
Systolic	157 ± 15.4	136.9 ± 20.6	0.004
Diastolic	80.8 ± 8.6	76.1 ± 10.4	NS
Post-dialysis			
Systolic	176.1 ± 15	130.5 ± 21.7	0.0001
Diastolic	86 ± 10.8	75.3 ± 10.2	0.008
Antihypertensive therapy (% of n)			
All kinds	47.4	36.8	0.01
Alpha blockers		21.1	NS
Beta-blockers	15.8	5.3	NS
ACE inhibitors and receptor blockers	15.8	5.3	NS
Calcium channel blockers	68.4	31.6	NS.

ACE = angiotensin-converting enzyme

Discussion

Various mechanisms leading to post-dialysis hypertension have been suggested. Lins et al. [13] concluded that ambulatory and post-dialysis blood pressure, but not pre-dialysis blood pressure, was significantly correlated with total body water percentage of dry weight, measured by body impedance analysis. This association was also observed in many of their PDHT patients.

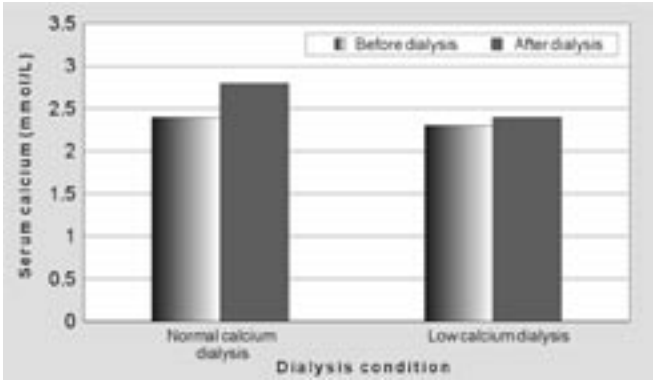

Figure 1. Serum calcium (mmol/L) pre- and post-dialysis, by dialysis condition. After 4 weeks treatment with low calcium dialysis, there was a significant reduction in mean post-dialysis serum total calcium (2.34 ± 0.2 vs. 2.86 ± 0.12 mmol/L, P = 0.04).

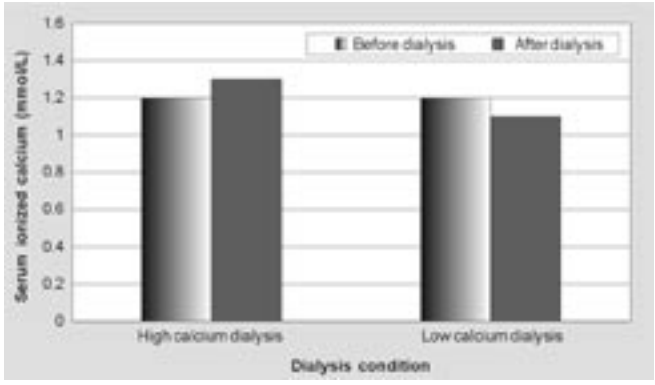

Figure 2. Serum ionized calcium (mmol/L) pre- and post-dialysis, by dialysis condition. Mean post-dialysis serum ionized calcium was also significantly reduced after the 4 week intervention with low calcium dialysis (1.17 ± 0.12 vs. 1.3 ± 0.06 mmol/L, P = 0.03).

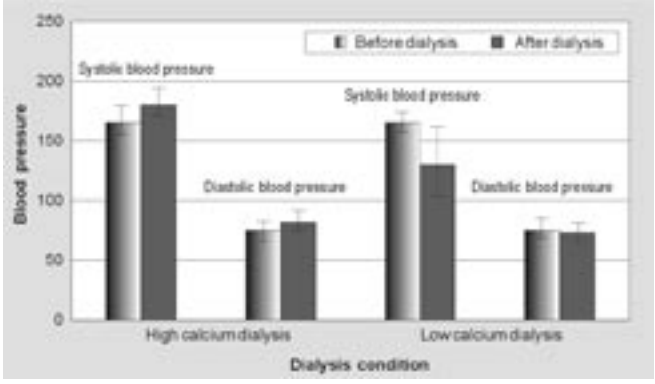

Figure 3. Systolic and diastolic blood pressure (mmHg) before and after dialysis by dialysis condition. Baseline post-dialysis blood pressure was significantly higher than post-dialysis blood pressure after the 4 week low calcium intervention (176 ± 15/86 ± 10.8 mmHg vs. 134.1 ± 20.8/80 ± 8.6 mmHg, P = 0.001). On the other hand, pre-dialysis blood pressure in PDHT patients (157.9 ± 15.4/80.8 ± 8.6 mmHg) did not significantly differ from pre-dialysis measurements after 4 weeks of low calcium dialysis (155.3 ± 9.7/82 ± 7.9 mmHg).

An acute decrease in serum potassium during low potassium hemodialysis caused a significant increase in blood pressure 1 hour post-dialysis ("rebound hypertension") in 11 normokalemic normotensive patients [14]. Nitric oxide production was found to be reduced during hemodialysis but without any related effect on arterial blood pressure [15].

Of the 127 maintenance hemodialysis patients in our department, 16% had PDHT. These 19 patients ("calcium sensitive"?) were significantly older and were prescribed more antihypertensive medications than were non-PDHT patients ("calcium resistant"?). Their older age may contribute to their higher basal blood pressure by a possible more profound atherosclerosis. Post-dialysis blood pressure levels in the PDHT patients reached the borderline of severe hypertension (176 ± 15/86 ± 10.8 mmHg) [12]. Although the difference in years of dialysis (3.6 years in the PDHT group vs. 5.16 years in non-PDHT patients) is not significant, a residual renin release from "younger" native kidneys of PDHT patients could be another explanation for their basal higher levels of arterial blood pressure, related to the non-PDHT group. In this study neither plasma renin activity nor vascular resistance were measured. According to department protocol, PDHT patients were detained for not less than 2 hours after termination of the dialysis session until hypertensive symptoms were normalized and stabilization of blood pressure was achieved.

Hypercalcemia-related hypertension has been widely reported in association with prolonged immobilization, vitamin D intoxication and primary hyperparathyroidism [5,6,16]. Secondary hyperparathyroidism in chronic renal failure patients treated with calcium and vitamin D is associated with a reduction in the prevalence of hypercalcemia-induced hypertension. PTH acute injection to rats attenuates elevated blood pressure via its angiotensin II inhibitory effect, causing vasodilatation [1,4,17]. In end-stage renal failure patients, the hypertensive effect of hypercalcemia is not diminished by secondary hyperparathyroidism, which is chronic. Furthermore, by increasing atherosclerosis, PTH enhances peripheral vascular resistance [16,18]. Further support for the role of calcium in hemodynamic homeostasis in hemodialysis patients is provided by Alappan and colleagues [19] who found that the addition of high calcium dialysate concentration (1.75 mEq/L) to midodrine and/or cool dialysate improved blood pressure in patients with intradialytic hypotension. However, this therapy did not reduce intradialytic hypertension symptoms or the interventions required to treat them. In addition, 22% of the patients suffered from adverse effects of hypercalcemia. Treating our PDHT group with low calcium dialysis caused not only normalization of PDHCa but also the prevention of symptomatic hypertension at its end. This treatment was not associated by acute changes in iPTH levels.

It has been shown that lowering the dialysate calcium concentration to 1.5 and 1.25 mmol/L to treat hypercalcemia has neither acute nor long-term adverse effects in terms of cardiovascular stability, positive calcium balance maintenance and parathyroid function [10,20]. In cardiac-compromised patients, however, lowering the dialysate calcium concentration has

been reported to cause a significant decrease in cardiac output and left ventricular performance, leading to hypotension during dialysis [21]. Kyriazis et al. [22] reported that reducing the incidence of hemodialysis-induced hypercalcemia is beneficial in preventing the ongoing reduction of arterial compliance; however, they insist on a cautious use of low calcium dialysis, suggesting a dialysate calcium profiling strategy to prevent decrease of left cardiac output and thus abolish intradialytic hypertension [23]. None of our PDHT patients was cardiac-compromised and no hemodynamic insults occurred during or at the end of low calcium dialysis sessions.

In summary, we observed that 16% of hemodialysis patients in our unit (n=127) exhibited PDHT and PDHCa. These patients were older and more frequently prescribed antihypertensive medications than were non-PDHT patients. Treatment with low calcium dialysis for PDHCa prevented PDHT, without a parallel change in mean decrease of patients' body weight. Nevertheless, a controlled clinical trial examining the efficacy and safety of low calcium dialysis on PDHT is required.

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