

## TOTAL DIALYSATE CALCIUM EFFECTS ON CALCIUM BALANCE DURING DIALYSIS

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### Abstract

*Introduction:* Total dialysate calcium concentration has an important influence on calcium metabolism in bicarbonate high-flux dialysis.

The aim of the study is to investigate the influence of different dialysate calcium concentrations on serum concentration of ionised calcium and on the balance of total dialysate calcium.

*Materials and methods:* A total of 20 stable aneuric patients on chronic bicarbonate high-flux haemodialysis with a frequency of 4 hours, 3 times per week with two different concentrations of total dialysate calcium (tdCa) were included in the study. Dialysis in the first session was performed with total dialysate calcium of 1.25 mmol/L, and at the next session with dialysate calcium of 1.5 mmol/L. The serum concentrations of total and ionized calcium were determined before and after each dialysis session. The balance of total dialysate calcium was measured on the dialysate side.

*Results:* Serum concentration of total calcium before and after haemodialysis did not show any significant difference in HD with a total dialysate calcium of 1.25 mmol/L ( $2.40 \pm 0.19$  mmol/L before HD and  $2.46 \pm 0.15$  mmol/L after HD). Serum ionized calcium in HD with tdCa 1.25 significantly decreased after HD ( $1.16 \pm 0.09$  mmol/L before HD to  $1.08 \pm 0.04$  mmol/L after HD,  $p < 0.05$ ). The total serum calcium significantly increased after HD in comparison to HD with tdCa of 1.5 mmol/L ( $2.40 \pm 0.15$  mmol/L to  $2.65 \pm 0.16$  mmol/L,  $p < 0.05$ ). The concentration of serum ionized calcium did not increase significantly in HD with tdCa 1.50 mmol/L ( $1.16 \pm 0.08$  mmol/L to  $1.20 \pm 0.05$  mmol/L). Average values of total dialysate calcium balance (gradient of diffusion between dialysate and patient) were negative in tdCa 1.25 ( $1.38 \pm 0.08$  mmol/L versus  $1.48 \pm 0.43$  mmol/L), but in HD with tdCa 1.5 were slightly positive ( $1.56 \pm 0.07$  mmol/L versus  $1.52 \pm 0.07$ ).

*Conclusion:* The use of total dialysate calcium of 1.5 mmol/L is beneficial because balance values of total dialysate calcium are slightly positive, but serum concentration of ionized calcium stays in the normal range.

**Key words:** dialysate calcium, serum total calcium, ionized calcium.

### Introduction

The impairments of mineral and bone metabolism are one of the most important causes of high morbidity and mortality in chronic haemodialysis patients. Hyperparathyroidism, adynamic bone disease, osteomalacia and  $\beta_2$ -microglobulin amyloidosis are all conditions involving bone that may be observed in chronic

haemodialysis patients. The main factors influencing the secretion of parathyroid hormone are calcium, phosphate and vitamin D<sub>3</sub>. Haemodialysis patients have disruption in systemic calcium and phosphate homeostasis. Hyperphosphataemia, low level of calcitriol and resulting hypocalcaemia are pathophysiological bases for the development of secondary hyperparathy-

roidism. On the contrary, a low level of parathormon, excessive administration of calcitriol and high intake of calcium phosphate binders (hypercalcaemia) are responsible for development of adynamic bone disease and metastatic soft tissue calcifications. Current guidelines recommend therapeutic strategies that are related to the application of phosphorus-binding agents, vitamin D analogues and calcimimetics [1]. However, in current clinical practice little attention is paid to dialysate calcium concentration. But recently, in a few studies, more connotation has been given in the measurement of calcium balance during haemodialysis.

Serum calcium is present in three different forms: ionized (about 45%), complexed (about 10%) and protein-bound protein (about 45%). Ionized and complexed calcium compose ultrafiltrable (diffusible) calcium that passes through the dialyzer membrane under the concentration gradient and hydrostatic pressure (convection). Protein bound calcium does not pass through the membrane, which makes it possible to calculate the complexed calcium concentration in dialysate from the difference between total dialysate calcium and ionized calcium [4]. The former provide calculation of calcium balance during dialysis on the dialysate site. No doubt exists that an inlet dialysate calcium concentration of 1.75 mmol/L leads to positive calcium balance, but this is controversial with dialysate calcium concentrations of 1.5 mmol/L and especially 1.25 mmol/L.

The reason for measurements of calcium balance during haemodialysis performed by different concentrations of dialysate calcium, is to achieve a neutral or mild positive calcium balance, to preserve serum calcium in the normal range, to keep the level of parathormon (PTH) 2–3 times above the normal values and to prevent the appearance of calcification in soft tissues [1, 2].

#### **Aim of study**

- To investigate the influence of two different dialysate calcium concentrations upon intradialysis calcium balance and serum calcium concentrations.
- To see what dialysate calcium concentration can be accepted as standard, and optimal for the majority of patients on maintenance haemodialysis.

#### **Materials and methods**

A total of 20 stable aneuric maintenance haemodialysis patients were included in the study. All the patients were free of clinical signs of cardiovascular comorbidity. The haemodialysis procedures were performed using synthetic (polyethersulfon) high flux membranes, sterilized by gamma rays. Haemodialysis parameters (blood and dialysate flows, individualized dialysate composition with respect to sodium and bicarbonate) were adapted to achieve optimal urea clearance, ultrafiltration and acid balance. Every HD session lasted 4–5 hours and the frequency was 3 times per week. Serum calcium concentration (total and ionized) and phosphate in all patients were not significantly different before the sessions (Table 1). Assessment was made in two subsequent HD sessions, each made with a different dialysate calcium concentration (dCa): dialysate calcium 1.25 mmol/L (dCa 1.25) and dialysate calcium 1.50 mmol/L (dCa 1.50). Before and after each HD session, blood samples were drawn to determine serum calcium concentration (total and ionized) and phosphate.

During the first, second and fourth hour of HD session, samples of dialysate were taken to determine total and ionized calcium concentration and phosphate, in fresh and spent dialysate. A twelve-lead electrocardiogram (ECG) was made before and after each session in all patients, and blood pressure (BP) and heart rate (HR) were measured every hour during the session.

Statistical analysis was made using SPSS 16.0 statistical software. Data are presented with mean values and standard deviations. To analyze the differences before and after dialysis, a paired Student-T test was used.

#### **Results**

Post dialysis, total serum calcium concentrations did not significantly change in patients on dialysis using both dialysate calcium concentrations. However, serum concentration of ionized calcium significantly decreased in patients on dialysis using dCa 1.25 mmol/L ( $1.16 \pm 0.09$  mmol/L vs  $1.08 \pm 0.04$  mmol/L,  $p < 0.05$ ) In patients on dialysis using dCa of 1.50 mmol/L, the concentration of serum ionized calcium remained unchanged (Table 1).

Table 1

*Pre- and post-dialysis values of serum electrolytes in 20 patients treated with dCa 1.25 and dCa 1.50*

Parameter	Before HD	After HD	Before HD	After HD
tCa mmol/L	2.40 ± 0.19	2.46 ± 0.15	2.4 ± 0.15	2.65 ± 0.16*
iCa mmol/L	1.16 ± 0.09	1.08 ± 0.04*	1.16 ± 0.08	1.20 ± 0.05
PO <sub>4</sub> mmol/L	1.82 ± 0.61	0.88 ± 0.36*	1.91 ± 0.57	1.05 ± 0.37*

dCa1.25

dCa1.50

tCa, Total calcium  
iCa, Ionized calcium  
\*p < 0.05

Average concentration of total calcium in the spent dialysis solution was higher in comparison to fresh dialysate when using dialysate with 1.25 mmol/L calcium concentration, indicating a negative calcium balance (Table 2, Fi-

gure 1). There was no significant difference in total calcium concentration in fresh and spent dialysate when using dialysate with 1.50 calcium concentration, indicating a slight positive calcium balance (Table 2, Figure 2).

Table 2

*Concentration of dCa on entrance site (fresh dialysate) and exit site (spent dialysate) in 20 patients treated with dca 1.25 and dCa 1.50*

Parameter	Entrance (fresh)	Exit (spent)	Entrance (fresh)	Exit (spent)
dtCa, mmol/L	1.38 ± 0.08	1.48 ± 0.43	1.56 ± 0.07	1.52 ± 0.07
diCa, mmol/L	1.06 ± 0.03	1.03 ± 0.04	1.21 ± 0.04	1.13 ± 0.03
dcCa, mmol/L	0.32 ± 0.07	0.35 ± 0.04	0.35 ± 0.04	0.40 ± 0.05
dPO <sub>4</sub> mmol/L	0.08 ± 0.11	0.60 ± 0.45	0.06 ± 0.07	0.60 ± 0.28

dCa1.25

dCa1.50

dtCa, Total dialysate calcium  
diCa, Ionized dialysate calcium  
dcCa, complex ionized calcium

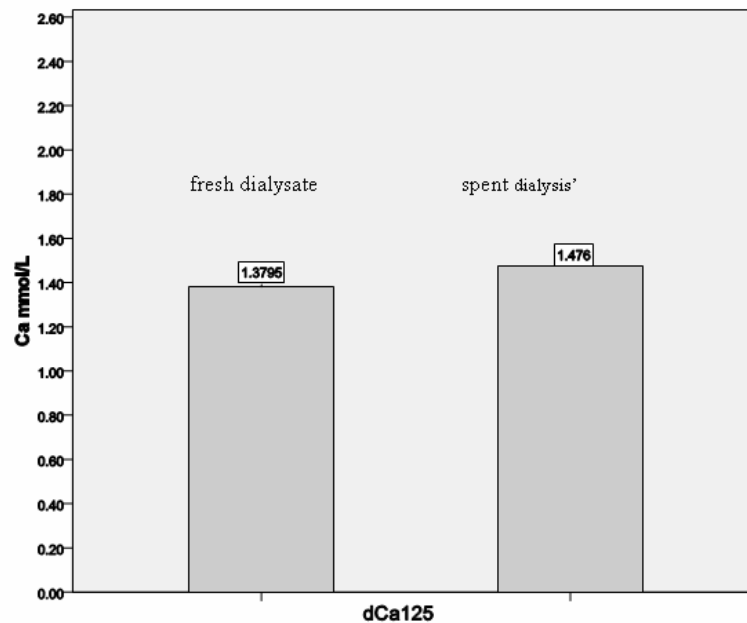


Figure 1 – Balance of calcium during HD with dCa 1.25. Total calcium concentration is higher in spent dialysate, demonstrating that there is negative calcium balance

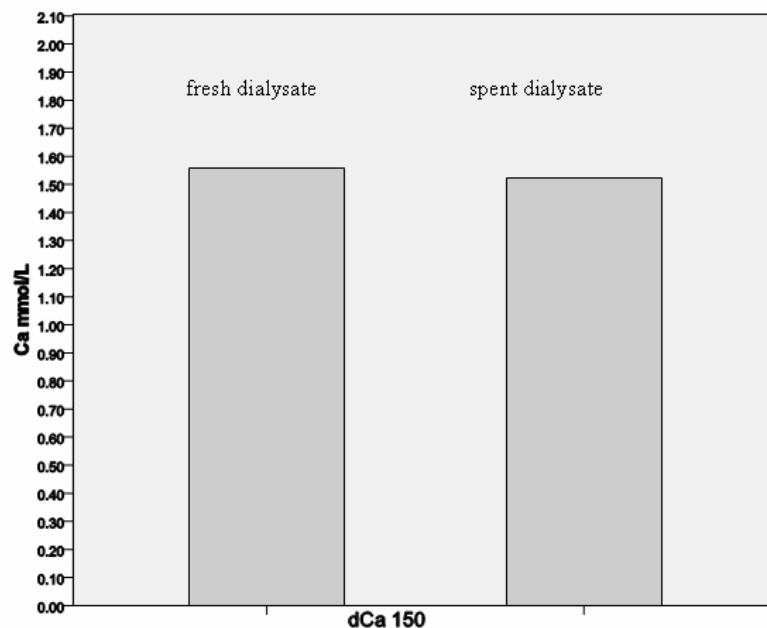


Figure 2 – Balance of calcium during HD with dCa 1.50. Concentration of total calcium in spent dialysate which pointed to neutral balance of calcium

The average concentration of ionized calcium in fresh and spent dialysate did not significantly change when using dialysate with 1.25 mmol/L calcium concentration. When using dialysate with 1.50 mmol/L calcium concentration, there was a significant decrease of ionized calcium in the spent dialysate, indicating a slight positive balance of ionized calcium. Table 2 shows an increase of complexed calcium in spent dialysate in HD sessions with a different dCa concentration.

Phosphate serum concentration significantly decreased after HD sessions with a different dialysate calcium concentration.

Phosphate concentration in the spent dialysate significantly increased, but there was no significant difference when using dialysate with different calcium concentrations.

During HD sessions using different dCa concentrations, no clinical signs of circulatory unstable conditions were detected. QTc intervals (Bazett's equation) significantly increased when using dCa 1.25 mmol/L in comparison to QTc intervals when dCa 1.50 mmol/L was used [3].

### Discussion

Table 2 shows that complexed calcium concentration is higher in spent dialysate in comparison to fresh dialysate. Probably, this

increase is due to calcium ions binding to a phosphate anion which are in higher concentration in spent dialysate. Additionally, ionized calcium also binds to other anions, such as lactate, citrate, bicarbonate and sulphate. Because of this, dialysis with dCa 1.25 mmol/L, where there is no significant difference in ionized calcium between fresh and spent dialysate, and the total calcium concentration is significantly higher in spent dialysate, the balance of calcium is not neutral, but negative (Table 2). That is why the assessment of calcium balance is calculated by the total, but not by the ionized calcium in the dialysate.

In our study pre-dialysis serum values of two calcium pools (total and ionized) were in the normal range. Haemodialysis performed with 1.25 dCa significantly decreased the concentration of ionized serum calcium (biologically active), but the balance of total dCa was negative. On the contrary, administration of dCa 1.50 mmol/L does not lead to an increase in concentration of serum ionized calcium, while the balance of total dCa is neutral. These findings are of particular importance to the long-lasting effects on parathyroid gland function. In fact, in a number of studies published it is shown that haemodialysis performed with low dCa (1.25 mmol/L) stimulates the parathyroid

gland and worsens secondary hyperparathyroidism and high turn-over bone mineral disease [5, 6]. On the other hand, haemodialysis performed with high dCa (1.75 mmol/L) leads to a positive balance of total calcium, increasing serum-ionized calcium and suppressing parathyroid gland function. In our study, dialysis performed with dCa 1.5 did not lead to changes of serum-ionized calcium, while the balance of total dCa was neutral, or slightly positive.

For the majority of patients, it seems that adequate concentration of dCa is 1,50 mmol/L, while lower dCa (1.25) and higher dCa (1.75) should be applied to selected patients and only temporarily [7–9].

From a practical point of view, in patients with positive calcium balance, a decrease of dCa concentration is needed in order to reach a neutral balance. However, in order to reduce dCa concentration, it is necessary to make an attempt to reduce the calcium excess by applying other measures: reduction of diet intake of calcium, decrease or change of calcium phosphate binders with non-calcium phosphate-binding agents, and modification of vitamin-D analogues doses.

If there are low serum PTH and adynamic bone disease, application of low dCa increases serum PTH and improves the adynamic bone disease.

In patients with secondary hyperparathyroidism and high turn-over bone mineral disease, a negative balance of calcium will lead to further worsening of the condition. These patients will need a high dose of active vitamin D, careful choice and dose of phosphate-binding agents and high concentration of dCa (1.75 mmol/L). At the same time, administration of calcimimetics (cinacalcet), which suppress parathyroid gland function and decrease the serum level of calcium and phosphate, enables the safe use of high dCa and other drugs which increase calcaemia (calcium binding phosphate agent, vitamin D) [10–12].

A high concentration of dCa is effective in controlling secondary hyperparathyroidism, but we should take into consideration the risk of harder suppression of PTH, the development of adynamic bone mineral disease, hypercalcaemia and the appearance of extraskeletal cal-

cifications (vascular, valvular and other soft tissues) [13].

Low dialysate calcium might be associated with frequent episodes of hypotension and disorders of heart rhythms. In our study, as in others, QTc interval was significantly increased by dialysis performed with dialysate calcium 1.25 mmol/L [3, 14]. Life-threatening ventricular arrhythmias during haemodialysis are possible, especially in patients with manifest cardiovascular comorbidity treated with dialysate calcium 1.25 mmol/l. Successful implementation of CKD-MBD guidelines shows significant improvement of all bone and mineral parameters presented in the multicentre study conducted in the Republic of Macedonia [15].

### Conclusion

The use of total dialysate calcium 1.50 mmol/L seems to be adequate and safe for the majority of patients, because the balance of total dialysate calcium is slightly positive, but the serum concentration of ionized calcium stays in the referent range. However, it should be emphasized that the choice of dialysate calcium concentration must be a part of an integrated therapeutic approach to control renal osteodystrophy and maintain the normal mineral metabolism (phosphate-binding agents, vitamin D analogues, calcimimetics).

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## Резиме

### ЕФЕКТИ НА ТОТАЛЕН ДИЈАЛИЗАТЕН КАЛЦИУМ ВРЗ КАЛЦИУМ БАЛАНС ВО ТЕКОТ НА ДИЈАЛИЗАТА

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Специјална болница за нефрологија и дијализа Диамед, Скопје, Р. Македонија

*Вовед:* Концентрациите на вкупниот дијализатен калциум (tdCa) значајно влијаат на мета-

болизмот на калциумот при бикарбонатна високо-проточна хемодијализа.

Целта на студијата е да се испита влијанието на разни концентрации на дијализатен калциум врз серумските концентрации на јонизираниот калциум и на вредностите на балансите на вкупниот дијализатен калциум.

*Материјал и методи:* Во студијата се вклучени 20 стабилни анурични пациенти на хронична бикарбонатна високо-проточна хемодијализа (ХД) три пати неделно по 4 часа со две различни концентрации на вкупен дијализатен калциум (tdCa). Дијализите во првата сесија беа изведувани со концентрација на вкупниот дијализатен калциум од 1,25 mmol/L, а во следната сесија со дијализатен калциум 1,5 mmol/L. Пред и по секоја дијализна сеанса беа одредени серумските концентрации на вкупниот и јонизираниот калциум. Балансите на вкупниот дијализатен калциум се мерени на дијализатната страна.

*Резултати:* Серумските концентрации на вкупниот калциум пред и по хемодијализата не покажаа значајна промена при изведување на ХД со вкупен дијализатен калциум од 1,25 mmol/L ( $2,40 \pm 0,19$  mmol/L пред ХД и  $2,46 \pm 0,15$  mmol/L по ХД). Серумскиот јонизиран калциум при ХД со tdCa 1,25 значајно се намали по дијализата ( $1,16 \pm 0,09$  mmol/L пред ХД на  $1,08 \pm 0,04$  mmol/L по ХД,  $p < 0,05$ ). Вкупниот серумски калциум значајно се зголеми по ХД во однос на вредностите пред ХД при изведување на ХД со вкупен дијализатен калциум од 1,5 mmol/L (од  $2,40 \pm 0,15$  mmol/L на  $2,65 \pm 0,16$  mmol/L,  $p < 0,05$ ). Концентрациите на серумскиот јонизиран калциум незначително се зголемија при користење на tdCa 1,5 mmol/L (од  $1,16 \pm 0,08$  mmol/L на  $1,20 \pm 0,05$  mmol/L). Средните вредности на балансот на вкупниот дијализатен калциум (градиентот на дифузија помеѓу дијализатот и пациентот) беа негативни при користење на dtCa 1,25 ( $1,38 \pm 0,08$  mmol/L наспроти  $1,48 \pm 0,43$  mmol/L), додека при користење на dtCa 1,5 беа лесно позитивни ( $1,56 \pm 0,07$  mmol/L наспроти  $1,52 \pm 0,07$ ).

*Заклучок:* Употребата на вкупен дијализатен калциум од 1,5 mmol/L има предност бидејќи вредностите на балансите на вкупниот дијализатен калциум се лесно позитивни, а серумските концентрации на јонизираниот калциум остануваат во рамките на референтните вредности.

**Клучни заборови:** дијализатен калциум, серумски вкупен калциум, јонски калциум.