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Kinetics of calcium, phosphate, and magnesium and PTH variations during hemodiafiltration

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SUMMARY

Hemodiafiltration (HDF) is a technique resulting from coupling of diffusive and convective transport and thereby increase the elimination of small and middle molecules. However, may induce a convective loss from others substances such as calcium and magnesium. The aim of this study was to evaluate the effects of Ultrafiltration on the kinetics of calcium, phosphate, magnesium and parathyroid hormone. A total of thirteen patients (7 males and 6 females) on hemodialysis, were studied. Each patient was randomly dialyzed with the same dialysate calcium concentration and three different ultrafiltration rate. Schedule A: High flux hemodialysis, schedule B: HDF with 10% of weight body and schedule C: HDF with 20% of weight body. The others parameters were kept identical. Total Ultrafiltration was 2.6 ± 0.9 L (9.78 ± 3.78 ml/min) in A, 9.3 ± 1.7 L (34.54 ± 6.22 ml/min) in B and 16.3 ± 3.3 L (60.94 ± 12.63 ml/min) in C. Replacement fluid during dialysis was 6.85 ± 1.42 and 13.65 ± 2.9 L. in C and C respectively. Posdialysis total, ionized calcium and magnesium were significantly lower in schedules B and C versus *A. PTH levels did not differ significantly. However, PTH changes during dialysis was -36.6 ± 38.6%, 6.3 ± 69.8% and 32.2 ± 63.2% in A, B and C, respectively ($p < 0.05$ A* vs *C). A significant inverse correlation was found between total Ultrafiltration and posdialysis levels of total calcium (r: -0.56, $p < 0.001$), ionized calcium (r: -0.65, $p < 0.001$) and magnesium (r:-0.47, $p < 0.01$). No differences were observed in pre and posdialysis phosphate levels, neither mass transfer and clearance of phosphate. We concluded that high ultrafiltration flow rates and substitution fluid without divalent cations induces a negative calcium and magnesium balance. These changes may stimulate PTH secretion during HDF. This technique did not resulte in a higher clearance or phosphate removal.*

Key words: ***Hemodiafiltration. Calcium balance. Parathyroid hormone. Ionized calcium. Phosphate. Magnesium.***

CINÉTICA DEL CALCIO, FÓSFORO, MAGNESIO Y VARIACIONES DE LA PARATHORMONA (PTH) EN PACIENTES EN HEMODIAFILTRACIÓN

RESUMEN

La hemodiafiltración (HDF) es una técnica que combina los mecanismos difusivo y convectivo para lograr mayor eficacia depurativa. La confluencia de ambos

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mecanismos puede dificultar la transferencia de sustancias como el calcio, cuyo gradiente difusivo sea líquido de diálisis-sangre. El objetivo de nuestro estudio fue valorar la importancia de la convección en la transferencias del calcio, fósforo, magnesio y la PTH. Se estudiaron 13 pacientes en programa de hemodiálisis. A cada paciente se le realizó en la sesión de mitad de semana y de manera aleatoria tres esquemas de hemodiálisis: Tipo A.: Hemodiálisis de alto flujo. Tipo B: HDF del 10% del peso seco. Tipo C: HDF del 20% del peso seco. Las características de la sesión de HD fueron las habituales en cada paciente. La concentración de calcio en el líquido de diálisis fue la misma en los 3 tipos de sesiones. La composición del líquido de sustitución era: Na 145 mEq/l, Cl 85 mEq/l, HCO3- 60 mEq/l. El monitor de hemodiálisis empleado fue Integra® que disponía del módulo Quantiscan. Se determinaron al inicio (pre-HD) y al final (pos-HD) de la diálisis, el calcio total, calcio iónico, fósforo, magnesio y PTH. En el líquido de diálisis recogido mediante el Quantiscan, se determinaron los niveles de fósforo. No encontramos diferencias significativas entre los tres tipos de sesión para las concentraciones de calcio total pre-HD, Ca++ pre-HD, Mg pre-HD, fósforo pre y pos-HD ni en la transferencia de masa de fósforo. El calcio total pos-HD fue 9,93 ± 0,75 en la sesión A, 9,30 ± 0,79 en la B y 8,79 ± 0,69 mg/dl en la C (p < 0,01 A vs *B y C). El Ca++ pos-HD fue de 2,61 ± 0,25 en la sesión A, 2,36 ± 0,27 en la B y 2,13 ± 0,28 mEq/l. en la C. (p < 0,01 A* vs *C). El Mg pos-HD 2,04 ± 0,11, 1,78 ± 0,14 y 1,77 ± 0,22 mg/dl, respectivamente (p < 0,001 A* vs *B y C). No se evidenciaron diferencias significativas en la PTH pre ni pos-HD. El porcentaje de variación de PTH durante la sesión fue de -36,6 ± 38,6% en la A, 6,3 ± 69,8% en la B y 32,2 ± 63,2% en la tipo C (p < 0,05 A* vs *C). La ultrafiltración total se correlacionó de manera inversa con los niveles séricos pos-HD, tanto de Ca total (r: -0,56, p < 0,001), Ca++ (r: -0,65, p < 0,001), como Mg (-0,47, p < 0,01). Concluimos que el incremento en las tasas de ultrafiltración con líquidos de sustitución carentes de cationes divalentes, originan un balance de calcio y magnesio negativo con descenso en los niveles séricos de estos cationes al final de la sesión. Estos cambios pueden provocar un incremento en los niveles de PTH. No hemos apreciado mejoría en las transferencias de masa de fósforo ni en su aclaramiento al aumentar la tasa de ultrafiltración.*

Palabras clave: ***Hemodiafiltración. Balance de calcio. PTH. Calcio iónico. Fósforo. Magnesio.***

INTRODUCTION

HDF is modality of dialysis offering high clearances of large and small molecules by combining high diffusion and convection flows.[1]

During HDF with a single dialyzer reciprocal influences will create between diffusion and convection that will condition calcium, phosphate, and magnesium transferences through the dialyzer membrane. High ultrafiltration rates make difficult the diffusing process of some of these ions from the dialysis fluid (DF) to the blood and may alter their balance if the replacement fluid lacks of these ions.[2,3]

The aim of this study was to assess the balance of the divalent ions calcium, magnesium, and phosphate, as well as the changes in the levels of parathyroid hormone (PTH) when ultrafiltration rates are increased during the HD session.

MATERIAL AND METHODS

Thirteen patients (7 males and 6 females), with a mean age of 72.5 ± 11.8 years and on a stable hemodialysis program three days per week were studied. Their dry weight was 68.6 ± 13.8 Kg. Their pre-HD weight was 70.7 ± 14 and post-HD weight 68.7 ± 13.7 Kg. Session duration was 270 ± 29.1 minutes. The average arterial flow (Qb) was 390 ± 50.26 mL/min and bath flow (Qd) was 737 ± 55.9.

Every patient was randomly submitted during the session of the mid-week to one of three dialysis schedules: A. High-flow hemodialysis with mandatory UF of the weight gained. B. Hemodiafiltration with added ultrafiltration of 10% of the dry weight. C. Hemodiafiltration with added ultrafiltration of 20 % of the dry weight.

In the three types of sessions a high permeability polyether sulphone dialyzer (Arylane H9®) of 2 m^2

was used. The calcium level in the DF was the same in the three types of sessions (10 patients, 3 mEq/L and 3 patients, 3.5 mEq/L). The magnesium level was 1 mEq/L in all cases.

The re-infusion fluid was a solution for hemodiafiltration, with the following composition: sodium 145 mEq/L, chloride 85 mEq/L, CO3H- 60 mEq/L.

The hemodialysis monitor used was Integra® that includes the Quantiscan module. This system allows for continuous gathering of representative samples of the whole dialysis fluid used. For this, it includes a low-flow peristaltic pump that takes the sample into a single use bag. In this way, at any time of the dialysis session it is possible to gather few milliliters of dialysis fluid that will allow us measuring the kinetics of the different solutes. Besides, it tells the total dialysis fluid volume that has passed through the dialyzer. Several studies have reported the usefulness of this method for directly quantifying urea clearances.[4, 5, 6]

Blood samples at the beginning and the end of the session (after decreasing the Qb down to 50 mL/min for 2 minutes) were taken for the analysis of total calcium total, ionic calcium, phosphate, magnesium, and PTH. Phosphate levels were determined in the dialysis fluid gathered by using the Quantiscan module.

The formulas used for quantifying the phosphate mass transference (MT) were as follows:

$$MT: V \times C$$

V: Total volume of dialysis fluid at the outlet of the dialyzer gathered by the QC.

C: Concentration of the substance.

Logarithmic mean of plasma phosphate level (Cm):

$$Cm = \frac{(Co - Cf)}{Ln\ (Co/Cf)}$$

Co: Patient's phosphate concentration pre-HD

Cf: Patient's phosphate concentration post-hemodialysis.

Phosphate clearance (K):

$$K = (TM/\ Cm \times t) \times 1{,}000$$

t: time of the HD session.

The device measures the total volume of dialysis fluid used and the volume of the sample gathered (Qs) is calculated by the module applying the following formula:

$$Qs = K \times (\ Qd + Quf + Qinf\ ) \times 0.001$$

K being 1 when Qd was 500 mL/min and K = 0.667 when the Qd used was 750 mL.

Calcium determination was done with an analyzer of blood gases (IL 1640) within the 10 minutes following the sample extraction. This parameter was only determined in 8 patients. The determination of total Ca, P and Mg was done by spectrophotometry with the Olympus Auto-analyzer 2700 and that of PTH by enzyme immunoassay with Immulite 2000 Auto-analyzer.

Statistical analysis

The results are expressed as mean ± standard deviation. Adjustment of variables to a normal distribution was done by the Kolmogorov-Smirnov test. The Pre-HD vs. Post-HD differences were analyzed by the Student's t test for paired samples. The differences between the three types of sessions were analyzed by using the analysis of variance and if the result were significant the Neuman-Keuls technique was applied. The relationship between the numerical variables was determined by Pearson's correlation analysis. A p value < 0.05 was considered statistically significant.

RESULTS

Total ultrafiltration done was 2.6 ± 0.9 L (9.78 ± 3.78 mL/min) with schedule A, 9.3 ± 1.7 L (34.54 ± 6.22 mL/min) with schedule B, and 16.3 ± 3.3 L (60.94 ± 12.63 mL/min) with schedule C. The volume of infused fluid during schedules B and C was 6.85 ± 1.42 and 13.65 ± 2.9 L, respectively.

The values of total Ca, Ca++, Mg and P at the beginning and the end of the session with the three treatment schedules are shown in Tables I and II. A significant increase in total calcium and Ca++ post-HD values as compared with pre-HD values was observed only with schedule A, and a decrease in P and Mg++ post-HD with the three schedules. Total calcium, Ca++, and Mg at the end of the session were lower with both types of HDF as compared with HDAF ($p < 0.01$). We did not find significant differences in serum P values with any of the treatment schedules. Figures 1 and 2 show the PTH values and the percentage of variation through the session with the three dialysis schedules. Post-HD PTH values were significantly increased during the session, as compared with the pre-HD values, only with sche-

Table I. Total Ca and Ca^{++} values at the beginning and the end of the session with the three treatment schedules

	Type A	Type B	Type C	p
Tot. Ca. Pre-HD (mg%)	9.03 ± 0.59	8.91 ± 0.58	8.87 ± 0.79	ns
Tot. Ca. Pos-HD (mg%)	9.93 ± 0.75*	9.30 ± 0.79	8.79 ± 0.69	< 0.01
Ca^{++} Pre-HD (mEq/L)	2.31 ± 0.21	2.18 ± 0.15	2.14 ± 0.19	ns
Ca^{++} Pos-HD (mEq/L)	2.61 ± 0.25*	2.36 ± 0.27	2.13 ± 0.28	< 0.01

*$p < 0.01$ *vs* Pre-HD.

dule C ($p < 0.05$). A trend towards an increase in PTH values when increasing the convection volume is observed although no significant differences were observed. By contrast, an increase in the percentage of PTH change during the session as the volume of infusion fluid increases is observed, and thus of the convection needs. Post-HD PTH values were negatively correlated with post-HD Ca++ values (r: -0.61; $p < 0.01$). We did not observe a significant correlation between PTH and Mg values at the end of the session.

The mass transference of phosphate was 994.1 ± 343.3 mg, 963.7 ± 388.3 mg, and 882.7 ± 320.5 mg for schedules A, B, and C, respectively (N.S.). Mean phosphate clearance was 135.8 ± 50.9 mL/min with no significant differences between the three schedules studied.

Total ultrafiltration was negatively correlated with post-HD serum levels of total Ca (r:-0.56; $p < 0.001$), Ca++ (r: -0.65; $p < 0.001$), and Mg (-0.47; $p < 0.01$).

DISCUSSION

Calcium gain in HD patients is produced from diffusion of this cation from the dialysis fluid to the blood. This process will depend on the concentration gradient between both compartments and on the mass transference of the dialyzer.[7]

However, in every HD session not only diffusive processes are implicated but also within the dialyzer itself a convective process is generated aimed at clearing the excess of water and sodium from the patient. The convective process is extraordinarily increased with HDF techniques.[8]

The combination of diffusion and convection interacting within the same dialyzer makes that the substances following a diffusive blood-DF gradient will be clearly improved and, by contrast, those with a diffusive DF-blood gradient will be impaired. Calcium and bicarbonate behave in the second way. Thus, intra-dialysis calcium gain can be seriously compro-

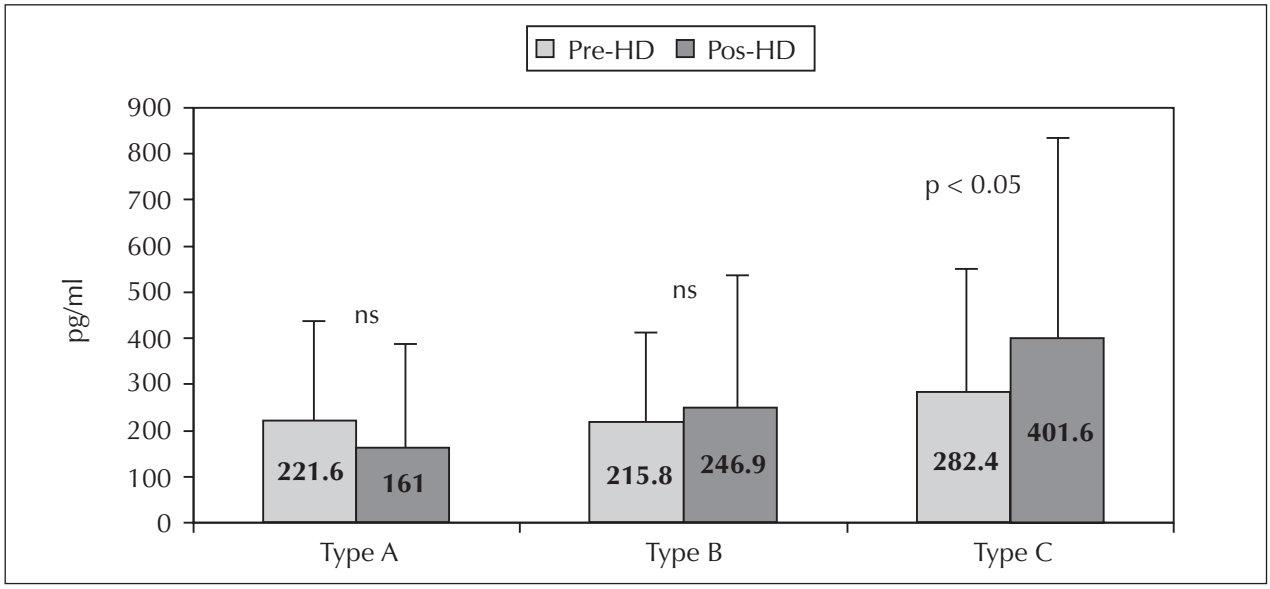

Fig. 1.—Serum PTH levels at the beginning and the end of the three types of sessions carried out.

Table II. Phosphate and Mg values at the beginning and the end of the session with the three treatment schedules

	Type A	Type B	Type C	p
Phosphate Pre-HD (mg%)	3.53 ± 0.97	3.59 ± 1.13	4.2 ± 1.11	ns
Phosphate Pos-HD (mg%)	2.08 ± 0.55**	1.84 ± 0.46**	2.03 ± 0.47**	ns
Mg Pre-HD (mg%/L)	2.30 ± 0.27	2.28 ± 0.29	2.36 ± 0.29	ns
Mg Pos-HD (mg%/L)	2.04 ± 0.11*	1.78 ± 0.14**	1.77 ± 0.22**	< 0.001

*p < 0.01 *vs* Pre-HD. **p < 0.001 *vs* Pre-HD.

mised if re-infusion fluids used do not contain the appropriate concentration and type of substance.[9,10]

During HDAF, post-HD levels of total Ca and Ca++ are significantly increased as a result of diffusive gain from the dialysis fluid. By contrast, no significant differences were observed with HDF schedules. The increase in the ultrafiltration rate makes difficult the transference of this cation. The negative correlation between the UF rate and post-HD Ca levels corroborates this fact. The use of a replacement fluid with an appropriate calcium concentration may solve this problem.[9] In most of our patients (n = 10), we used a fluid with calcium concentration of 3 mEq/L. Other authors have shown that calcium transference becomes negative when ultrafiltration rates are higher than 55 mL/min, using calcium concentrations of 3.5 mEq/L in the dialysis fluid. [3] Besides, de Vicenzi *et al*. showed that patients with acetate-free biofiltration (AFB) and UF rate of around 44 mL/min achieved a positive calcium balance by using Ca concentrations in the DF of 4 mEq/L.[11]

Serum Mg levels also significantly decreased during the HD session, although this descent was greater with HDF schedules. Moreover, they observed a negative correlation between Post-HD Mg serum levels and the UF rate. Mg changes during HD essentially depend on the concentration of this cation in the DF.[12,13] Our results confirm that convection also originates a negative balance of this cation, independently of the concentration existing in the DF.

We did not find significant differences in post-HD serum levels, mass transference, or phosphate clearance between the three schedules studied. In a previous study from our group, we did not detect changes in the percentage of phosphate reduction by increasing the ultrafiltration rate and later re-infusion at different blood flows in patients with on-line HDF.[14] Other authors have shown an increase in phosphate clearances with HDF as compared with HDAF.[15,16] However, prospective studies in the intermediate and long term do not show differences in this anion after switching the schedule from HDAF to high-convection HDF.[17,18,19] The biphasic kinetics of phosphate during HD and the influence of multiple factors make its quantification difficult.[20,21]

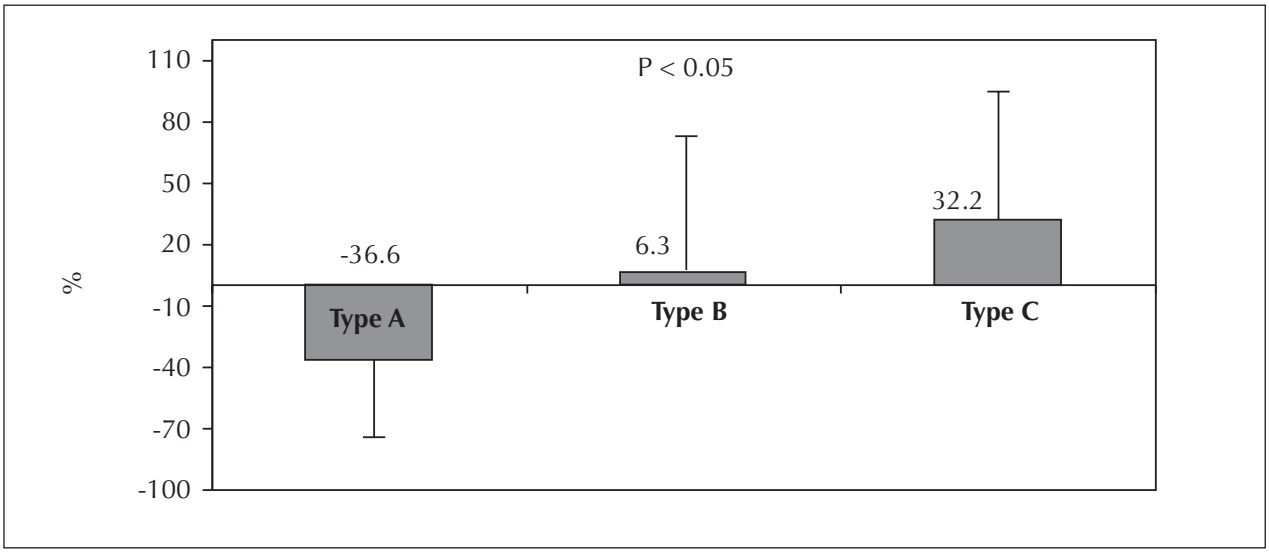

Fig. 2.—Percentage of change in serum PTH levels pre- and post-HD with the three types of schedules studied.

Several mechanisms may induce changes in PTH values during the hemodialysis session. Among these mechanisms, the changes in calcium and phosphate concentration, and even the clearance of the PTH molecule.[9, 22, 23] In our study, post-HD PTH values were only correlated with post-HD Ca++ levels. It is likely that the negative Ca balance as the result of high UF rates, together with a replacement fluid free from calcium, are the cause of the increase in PTH levels at the end of the session. These findings suggest a possible beneficial effect of high convection in those patients presenting adynamic bone disease with relative hyperparathyroidism, since PTH secretion is stimulated while an improvement in depurative efficacy is achieved.

We conclude that the increase in ultrafiltration rates with replacement fluids free from divalent cations produces a negative calcium and magnesium balance with a decrease in their serum levels at the end of the session. These changes may produce an increase in PTH levels. We have not observed an improvement in phosphate mass transference or in its clearance by increasing the ultrafiltration rate.

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