Calcium and phosphorus parameters and their association with serum parathormone in chronic kidney patients on hemodialysis

Parámetros de calcio y fósforo y su asociación con la parathormona sérica en pacientes renales crónicos en hemodiálisis

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ABSTRACT

The objective of this study was to investigate the association between calcium and phosphorus parameters with serum parathormone concentrations in patients with Chronic Kidney Disease (CKD) undergoing hemodialysis. It is descriptive quantitative cross-sectional study. The sample was composed of 50 individuals distributed in: group with up to 5 years of hemodialysis and group with more than 5 years of hemodialysis. Food consumption was assessed using 24-hour dietary recall. Descriptive analysis of quantitative variables was presented as mean and standard deviation. Data analysis was performed using the SPSS program; Student “T” test, Fisher’s exact test and Pearson’s chi-square test were used, with significance level p <0.05. The groups presented adequate serum calcium concentrations and high concentrations of phosphorus and parathormone. Patients with more than 5 years of hemodialysis had a statistically higher serum parathormone level (p= 0.034); there was an association between longer hemodialysis time and higher serum phosphorus concentrations (p= 0.039). There was a moderate positive correlation between serum parathormone and phosphorus in the group with up to 5 years of hemodialysis (p= 0.012). It was concluded that the progression of CKD increases serum phosphorus and parathormone concentrations, reflecting the pathophysiological events and altered metabolic demand inherent to the pathology.

Keywords: Calcium; Chronic kidney disease; Hemodialysis; Parathormone; Phosphorus.
RESUMEN

El objetivo de este trabajo fue investigar la asociación de los parámetros de calcio y fósforo con las concentraciones séricas de parathormona en pacientes con enfermedad renal crónica (ERC) en hemodiálisis. Se trata de un estudio descriptivo, cuantitativo y transversal. La muestra estuvo constituida por 50 individuos distribuidos en: grupo con hasta 5 años en hemodiálisis y grupo con más de 5 años en hemodiálisis. El consumo de alimentos se evaluó mediante el recordatorio de 24 horas. El análisis descriptivo de las variables cuantitativas se presentó como media y desviación estándar de la media. El análisis de los datos se realizó mediante el programa SPSS; Se utilizó la prueba "T" de Student, la prueba exacta de Fisher y la prueba de chi-cuadrado de Pearson, con un nivel de significancia de p < 0.05. Los grupos mostraron concentraciones adecuadas de calcio sérico y altas concentraciones de fósforo y parathormona. Los pacientes con más de 5 años de hemodiálisis tenían un nivel de parathormona sérica estadísticamente más alto (p = 0.034); hubo una asociación entre un mayor tiempo de hemodiálisis y mayores concentraciones de fósforo sérico (p = 0.039). Hubo una correlación positiva moderada entre parathormona sérica y fósforo en el grupo con hasta 5 años de hemodiálisis (p = 0.012). Se concluyó que la progresión de la ERC aumenta las concentraciones séricas de fósforo y parathormona, reflejando los eventos fisiopatológicos y alteración de la demanda metabólica inherente a la patología.

Palabras clave: Calcio; Fósforo; Enfermedad renal crónica; Hemodiálisis; Parathormona.

INTRODUCCIÓN

La Enfermedad renal crónica (ERC) es un trastorno progresivo y crónico que afecta a varios órganos y sistemas del cuerpo, incluyendo la función del riñón. La ERC es causada por una variedad de condiciones subyacentes, como la diabetes, la hipertensión arterial, la infección crónica, entre otras. La ERC puede progresar hasta convertirse en falla renal crónica, lo que implica que el riñón ya no puede realizar sus funciones adecuadamente. En estos casos, es necesaria la hemodiálisis para ayudar a eliminar las toxinas del cuerpo y mantener la homeostasis.

MÉTODOS

El estudio fue descriptivo, cuantitativo y transversal. La muestra consistió en 50 pacientes distribuidos en dos grupos: el grupo de pacientes con menos de 5 años en hemodiálisis y el grupo de pacientes con más de 5 años en hemodiálisis. El consumo de alimentos se evaluó mediante el recordatorio de 24 horas. El análisis de los datos se realizó mediante el programa SPSS; Se utilizó la prueba "T" de Student, la prueba exacta de Fisher y la prueba de chi-cuadrado de Pearson, con un nivel de significancia de p < 0.05. Los grupos mostraron concentraciones adecuadas de calcio sérico y altas concentraciones de fósforo y parathormona. Los pacientes con más de 5 años de hemodiálisis tenían un nivel de parathormona sérica estadísticamente más alto (p = 0.034); hubo una asociación entre un mayor tiempo de hemodiálisis y mayores concentraciones de fósforo sérico (p = 0.039). Hubo una correlación positiva moderada entre parathormona sérica y fósforo en el grupo con hasta 5 años de hemodiálisis (p = 0.012). Se concluyó que la progresión de la ERC aumenta las concentraciones séricas de fósforo y parathormona, reflejando los eventos fisiopatológicos y alteración de la demanda metabólica inherente a la patología.

Palabras clave: Calcio; Fósforo; Enfermedad renal crónica; Hemodiálisis; Parathormona.
To check the adequacy of dietary intake of macronutrients, calcium and phosphorus, the following were adopted for:
energy (30 to 35 kcal / kg (≥60 years) or 35 kcal / kg (<60 years), protein (1.2 g / kg), carbohydrate (50 to 60%), lipid (30 to 35%), phosphorus (800 to 1000 mg / day) and calcium (up to 1000 mg / day)\textsuperscript{13,14,15,16,17}.

After analyzing the 3 days of the R24h, the distribution of macronutrients and minerals (calcium and phosphorus) was found to be normal, which were adjusted for intrapersonal and interpersonal variability, avoiding to changes generated by differences in energy consumption\textsuperscript{18,19,20}. First, the data for this research was organized in Excel\textsuperscript{®} spreadsheets. Next, data were transferred to SPSS program (Windows\textsuperscript{®} version 22.0) for statistical analysis of the results. The descriptive analysis of quantitative variables was presented as mean and standard deviation of the mean.

To verify normality, the Kolmogorov-Smirnov test was applied. Student T test was used to compare the averages for parametric variables. In the analysis of correlations, considering the normal distribution of data, Pearson’s linear correlation coefficient was used. Chi-square test, Fisher’s exact test and Phi coefficients were used to study categorical variables. In all tests, the difference was considered statistically significant when the p value was <0.05, with a 95% confidence interval. The results were presented in tables and graphs.

The project was approved by the Research Ethics Committee of the Federal University of Piauí, number 2,527,329 and CAAE number 82702617.8.0000.5214. The study was carried out according to research ethics legislation for human beings (Resolution 466/2012). To perform data collection, consent was requested from the center chosen as the research site. By agreeing to participate in the research, participants signed an informed consent form and had the benefit of receiving their mineral calcium and phosphorus profile, in order to adopt intervention measures to curb the negative impact of mineral imbalance induced by CKD.

### RESULTS

This study included 50 patients in the age group between 23 and 76 years old, who were separated into: group with up to 5 years of HD (24 patients) and group with more than 5 years of HD (26 patients). Among patients with less than 5 years of HD, 66.7% (n= 16) were male and 33.3% (n= 8) female. In relation to those with more than 5 years, 73.1% (n= 19) were male and 26.9% (n= 7) female.

Mean values and standard deviations of age and anthropometric parameters used in the assessment of nutritional status of the participants are shown in table 1. Patients with up to 5 years of HD had body weight and BMI statistically higher than those who had HD more than 5 years (p= 0.005 and p= 0.010, respectively).

Mean values and standard deviations of food consumption: energy, macronutrient, phosphorus and calcium intake of study participants is shown in table 2. There was no statistically significant difference between groups regarding the intake of energy, protein, carbohydrate, lipid, calcium and phosphorus.

Table 3 shows the serum concentrations of calcium, phosphorus and PTH in both groups. Patients with more than 5 years of HD had a statistically higher serum PTH level, compared to those who in the up to 5 years HD group (p= 0.034).

Table 4 shows the percent adequacy of participant calcium and phosphorus intake, according to HD group. There was no statistically significant difference between groups (p= 0.340) for calcium. There was an association between longer HD time and high serum phosphorus concentrations (p= 0.039).

Table 5 shows the results of the linear correlation analysis between serum and dietary calcium and phosphorus concentrations and serum PTH in patients with CKD on HD. There was a moderate and significant positive correlation between the serum concentration of phosphorus and PTH, in the group of patients with up to 5 years of HD (p= 0.012).

### Table 1. Mean values and standard deviations of age, body weight, height and body mass index of the group with up to 5 years hemodialysis and participants with more than 5 years hemodialysis. Teresina-Piauí, Brazil, 2019 (Average ±SD).

| Parameter        | Up to 5 years HD (n= 24) | Over 5 years HD (n= 26) | p-value |
|------------------|--------------------------|-------------------------|---------|
| Age (years)      | 54.2±10.7                | 50.8±15.2               | 0.351   |
| Body weight (kg) | 66.4±13.4                | 56.8±9.7                | 0.005*  |
| Height (m)       | 1.63±0.09                | 1.61±0.08               | 0.321   |
| BMI (kg/m\(^2\)) | 24.88±3.77               | 22.03±3.73              | 0.010*  |

*Values significantly different among patients with chronic kidney disease undergoing dialysis with up to five years or more, Student t test (p <0.05). BMI= body mass index; HD= hemodialysis.
Table 2. Mean values and standard deviations of energy intake, macronutrients, phosphorus and calcium of patients with chronic kidney disease on HD. Teresina-Piauí, Brazil, 2019 (Average ±SD).

| Parameter                  | Up to 5 years HD (n= 24) | Over 5 years HD (n= 26) | p-value |
|----------------------------|---------------------------|-------------------------|---------|
| Energy (Kcal)              | 1236±514                  | 1269±325                | 0.790   |
| Carbohydrate (%)           | 53.1±8.1                  | 51.8±6.8                | 0.555   |
| Protein (%)                | 21.3±4.2                  | 19.6±3.0                | 0.112   |
| Lipids (%)                 | 25.6±7.2                  | 28.5±5.8                | 0.121   |
| Dietary phosphorus (mg/day) | 720±141                   | 668±151                 | 0.215   |
| Dietary calcium (mg/day)   | 308±133                   | 271±85                  | 0.239   |

Student t test (p <0.05). HD= hemodialysis. Reference values: 30 to 35 kcal/kg/day; 50 to 60% carbohydrates; 1.2 g/kg protein; 30 to 35% lipids; 800 to 1000 mg/day phosphorus; up to 1000 mg/day calcium.

Table 3. Mean values and standard deviations of calcium, phosphorus and parathormone of patients with chronic kidney disease on HD. Teresina-Piauí, Brazil, 2019 (Average ±SD).

| Parameter     | Up to 5 years HD (n= 24) | Over 5 years HD (n= 26) | p-value |
|---------------|---------------------------|-------------------------|---------|
| Calcium       | 9.03±0.53                 | 9.34±0.77               | 0.106   |
| Phosphorus    | 5.89±2.32                 | 5.68±1.48               | 0.717   |
| Parathormone  | 394±414                   | 742±672                 | 0.034*  |

* Values significantly different among patients with chronic kidney disease undergoing hemodialysis with up to five years or more, Student t test (p <0.05). HD=hemodialysis. Reference values: Calcium=8.4 to 10.2 mg / dL; Phosphorus=2.5 to 4.5 mg / dL; Parathormone ≤110 pg / ml.

Table 4. Percentage adequacy of calcium and phosphorus of participants, according to the time of HD. Teresina-Piauí, Brazil, 2019.

| Mineral   | Adequacy | Up to 5 years HD | Over 5 years HD | p-value |
|-----------|----------|------------------|-----------------|---------|
| Calcium   | Adequate | 83.3%            | 77%             | 0.340   |
|           | Inadequate | 16.7%           | 23%             |         |
| Phosphorus| Adequate | 41.7%            | 15.4%           | 0.039*  |
|           | Inadequate | 58.3%           | 84.6%           |         |

HD: Hemodialysis. Calcium: 8.4 to 10.2 mg/dl; Fisher's exact test; 16.7%=12.5% hypocalcemic and 4.2% hypercalcemic; 23%=19.2% hypercalcemic and 3.8% hypocalcemic; 83.3% + 16.7%=100%; 77% + 23%=100%. Phosphorus: 2.5 to 4.5 mg/dl; Pearson's Chi-square test (p<0.05), Phi coefficient (29.2%); 41.7% + 58.3%=100%; 15.4% + 84.6%=100%.
DISCUSSION

The predominance of males in this research was similar to some studies found\textsuperscript{21,22}, suggesting that men are more vulnerable to the progression of kidney disease and the need for HD, as they reveal a more negligent behavior regarding looking for health services in early stages of symptoms, present higher intake of caloric foods rich in fats and a higher frequency of alcohol consumption\textsuperscript{23}.

By stratifying the sample according to the duration of HD treatment, it can be seen that patients with a shorter duration of HD had a statistically higher weight and BMI than those who had been on HD for a longer time (Table 1), signaling more significant nutritional wear as therapy extends over time, as nutrient plunder and metabolic changes intensify that cause protein catabolism and depletion of lean and fat mass, as well as uremia, causing weight loss and lack of appetite\textsuperscript{24}.

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The evaluation of food consumption indicates that all nutrients (except carbohydrates) had a high probability of nutritional inadequacy, which may suggest that the present sample did not follow the specific dietary guidelines for patients with CKD on HD, or the impact of the pathology interfered in food consumption. In this perspective, the loss of appetite caused by the disease and HD, hormonal changes and inflammation contribute to the deficit in food consumption of these patients\textsuperscript{21,25,26}.

Inadequate consumption of energy and protein (Table 2) corroborates the results of some research\textsuperscript{25,26,27}. Rodrigues et al.\textsuperscript{21} obtained adequate consumption of phosphorus, protein, carbohydrate and lipid, but inadequate consumption of calcium and energy.

According to Rouhani et al.\textsuperscript{28} the energy density of the diet may indicate the risk of developing a higher stage of CKD. It is noteworthy that in patients undergoing HD, sufficient energy consumption can promote protein balance and consequently improve the performance of HD\textsuperscript{24}.

It is appropriate to call attention to the inadequacy in dietary intake of calcium and phosphorus in both groups, with no significant difference; which is with some studies\textsuperscript{29,30}. Low dietary calcium intake can be attributed to the insufficient consumption of milk and dairy products and other foods that are sources of calcium\textsuperscript{14}. A study has shown that insufficient calcium consumption may be due to the limitation of consumption of phosphorus-based foods, which are also rich in calcium and protein\textsuperscript{10}.

It should be noted that, despite the inadequate dietary intake of phosphorus, most patients in both groups analyzed presented hyperphosphatemia, which suggests

| Parameter | Up to 5 years hemodialysis | Over 5 years hemodialysis |
|-----------|---------------------------|--------------------------|
|           | r  | p               | r  | p               |
| SERUM CALCIUM |     |                 |     |                 |
| Dietary calcium | 0.231 | 0.279 | 0.214 | 0.293 |
| Serum phosphorus | -0.367 | 0.078 | 0.122 | 0.553 |
| Dietary phosphorus | 0.022 | 0.919 | 0.075 | 0.715 |
| SERUM PHOSPHORUS |     |                 |     |                 |
| Dietary phosphorus | -0.153 | 0.475 | 0.006 | 0.979 |
| Dietary calcium | -0.134 | 0.533 | 0.114 | 0.580 |
| PARATHORMONE |     |                 |     |                 |
| Serum phosphorus | 0.502 | 0.012* | 0.374 | 0.065 |
| Serum calcium | -0.148 | 0.489 | 0.008 | 0.970 |
| Dietary phosphorus | 0.097 | 0.651 | 0.053 | 0.803 |
| Dietary calcium | -0.101 | 0.639 | -0.031 | 0.885 |

* Significant correlation; Pearson's linear correlation coefficient (p <0.05). HD= hemodialysis. Dietary calcium (mg/day), serum calcium (mg/dL). Dietary phosphorus (mg/day), serum phosphorus (mg/dL). Parathormone (pg/mL).
the ineffectiveness of renal phosphorus excretion due to renal function failure. Furthermore, it reveals that the HD procedure does not efficiently remove serum phosphorus, due to its high molecular weight\textsuperscript{31,30}. In this context, the low dietary intake of phosphorus found can benefit the homeostasis of calcium and phosphorus in the conservation of bone mass, by compensating the competitive mechanism existing between these minerals and contributing to maintain the level of serum phosphorus up to the limit of 4.5 mg/dL\textsuperscript{31,33,15}. As an effective strategy, it is recommended to use phosphate binders, calcium supplements and vitamin D to minimize the effects of phosphorus retention on bone integrity\textsuperscript{37,32}.

Fifty-two percent (52\%) of the sample had been undergoing HD for more than 5 years; some participants in this study used calcium supplements (1 mcg/mL calcitriol) and phosphorus chelator (sevelamer hydrochloride active ingredient 800 mg on anhydrous basis). The adequacy of dialysis by means of fractional urea clearance (Kt/V) reached values of 1.5 to 2.0. Venous access was performed through arteriovenous fistula, and among the catheters, permcath in the jugular and double lumen were the most used\textsuperscript{31}.

Food consumption related to minerals, calcium and phosphorus, does not seem to have influenced respective serum levels, since there was no significant correlation between mineral content evaluated in the diet and serum concentrations. It is known that there are factors that affect the bioavailability of minerals, such as fiber consumption, dietary energy density, physiological states and the endogenous status of the minerals\textsuperscript{14}. Thus, analyzing the influence of diet on serum mineral levels is very complex, and the disease in question can precipitate profound changes in mineral levels, due to its pathophysiological events and altered metabolic demand\textsuperscript{33,15}.

The groups showed adequate mean values for calcium and high values for phosphorus and PTH (Table 3). Lehmkuhl et al.\textsuperscript{34} obtained similar results. The study by Barros et al.\textsuperscript{35} elevated serum levels of calcium, PTH and phosphorus in patients with a longer duration of HD, corroborating with this study only in terms of phosphorus and PTH levels.

Furthermore, hypocalcemia manifested itself in 12.5\% and 3.8\% of the sample, in the group with up to 5 years of HD and in the group with more than 5 years in HD, respectively, with no significant difference between groups; and hyperphosphatemia was statistically superior in the group with the longest treatment (p = 0.039) (Table 4). This result is attributed to the ineffectiveness of the treatment in removing serum phosphate and greater phosphorus retention, due to the progression of the disease and the bone remodeling condition\textsuperscript{16,37}. Another study\textsuperscript{37} found adequate serum phosphorus concentration, contradicting the results of this research.

The average level of PTH was inadequate in both groups, being higher in the group with longer duration of HD (Table 3), since the disease progression aggravates the disorders inherent to this pathology. Tentori et al.\textsuperscript{38} also observed a concentration of PTH above the recommended in the studied population, corroborating this research.

There was a moderate and significant positive correlation between serum PTH and phosphorus in the group with up to 5 years HD (Table 5), showing that the higher the serum phosphorus concentrations, the higher the PTH concentrations. This result is explained by the fact that the minerals, phosphorus and calcium, exercise competitive mechanisms; high phosphorus rates culminate in the excretion of calcium, that is, hyperphosphatemia results in the development of hypocalcemia, which is perceived by the parathyroid, which secretes PTH in an attempt to regulate the serum concentrations of this mineral. This mechanism is a risk to bone metabolism because it promotes mineral and bone disorders of chronic kidney disease (CKD-BMD) in the future; since, PTH in high amounts acts on the activation of 1α-hydroxylase and calcium reabsorption. Thus, high levels of serum phosphorus seem to cause an increase in PTH\textsuperscript{31,38,39}.

As CKD worsens, phosphate excretion remains active, causing a fall in tubular phosphate reabsorption, which occurs due to FGF-23 and PTH. However, in view of the proximal deficiency of tubular klotho, the participation of FGF-23 to control phosphate levels is insufficient; and PTH becomes responsible for performing phosphorus homeostasis. However, in the final stages of kidney disease, PTH does not support this adaptation and hyperphosphatemia sets in, even with high levels of PTH and FGF-23\textsuperscript{40}.

**CONCLUSIONS**

The study shows higher concentrations of phosphorus and PTH with the prolongation of HD, suggesting that therapy is not effective in preventing metabolic endocrine changes that favor mineral and bone disorders in CKD. Despite resistance to the action of PTH with disease progression, the results showed a significant positive correlation between serum phosphorus and PTH only in patients with less HD time, suggesting that the prolongation of dialysis therapy may be effective to remove excess phosphorus and thereby delay the progression of CKD-BMD compared to the start of treatment.

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