Longitudinal Observations on the Mineral Metabolism of Dialysis Patients at the University Hospital

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A retrospective review was performed from November 2011 through June 2012 in 49 stable patients receiving ambulatory hemodialysis at the dialysis unit of the University Hospital in San Juan. Measurements of serum phosphate, serum calcium (corrected to albumin levels), intact parathyroid hormone (PTH), and pulse pressure were obtained at 3-month intervals over the course of a 9-month observation period. These longitudinal observations assessed the efficiency of treatment, with the objective being to determine the nature of and then implement such changes as would improve the patients' outcomes.

Thirty-three of the 49 patients appeared to have fairly good control of their PTH levels during the observation period. Sixteen patients had levels over 300 pg/ml, and, using Stata data analysis software, a linear relationship with phosphate levels was obtained ($p = 0.021$, $R2 = 0.1037$, adjusted $R2 = 0.0855$). Pulse pressure (PP) measurements obtained at each observation interval showed the following increases: 69% at 3 months, 65% at 6 months, and 57% at 9 months. Calcium-containing phosphate binders were used in one third of the population and vitamin D analogs in 50%.

A trend towards a rise in PP was observed as calcium levels increased over 9.5 mg/dl. It is concluded that those patients experiencing that rise need close supervision to avoid the increasing morbidity and mortality associated with mineral metabolism derangement. Wide PPs were observed in these patients during the 9 months of observation, denoting persistent arterial stiffness suggestive of an increase in calcium balance. [*P R Health Sci J 2015;34:93-97*]

Key words: Dialysis patients, Bone metabolism, Arterial stiffness

Early on in the course of treatment, the great majority of chronic kidney disease (CKD) patients demonstrate mineral and bone metabolism abnormalities. The main factors producing these abnormalities include calcitriol deficiency, phosphate retention, decreased numbers of calcium sensory receptors in the parathyroid gland, and skeletal resistance to the calcemic action of parathyroid hormone (PTH) (1). As kidney function decreases, phosphate excretion is reduced, serum phosphorous increases, and plasma calcium and calcitriol both decline. Low levels of calcitriol lead to the decreased absorption of calcium, stimulating PTH secretion. Similarly, hyperphosphatemia causes an increase in PTH (2, 3). Fibroblast growth factor 23 (FGF23) has also been implicated in the pathophysiology of metabolic bone disease in CKD (4). Elevated levels of FGF23 are observed in these patients as a response to hyperphosphatemia. All of these factors contribute to secondary hyperparathyroidism, and the clinical practice guidelines of *Kidney Disease: Improving Global Outcomes* (KDIGO) suggest that PTH levels in these patients should be maintained between 150 to 300 pg/mL (5). Patients with these disturbances, hyperphosphatemia, hypocalcemia, and hyperparathyroidism may develop bone pain, myopathy, tendon rupture, and an increased incidence of fractures.

Patients with CKD have a reduced ability to convert 25(OH) vitamin D into the active form, 1,25(OH)2 vitamin D (calcitriol) (6). Recent evidence shows that in addition to regulating phosphate and calcium levels, calcitriol is responsible for regulating other pathways in other tissues, including cardiovascular and endothelial tissues. Decreased vitamin D-receptor activation in cardiovascular tissues may lead to cardiovascular complications such as hypercalcemia, vascular and organ calcification, atherosclerosis, and cardiac hypertrophy (7). These abnormalities may then result in cardiac failure, ischemic heart disease, cardiac arrhythmias, and increased cardiac mortality (8).

Soft tissue and vascular calcifications have been reported in hemodialysis and peritoneal dialysis patients (9, 10). The accumulation of calcium in the heart and vasculature is a strong predictor of mortality in stage-5 CKD patients (11). Evidence suggests that hyperphosphatemia is a major factor in the development of metastatic calcifications in late-stage CKD patients. The use of phosphate binders in order to decrease phosphate levels diminishes the incidence of metastatic calcifications (12, 13). Various types of phosphate binders are currently used, among which are calcium-based and non-calcium–, non-aluminum–based phosphate binders. Recently there has been a preference for the use of non-calcium and non-aluminum binders because calcium-based binders may cause a positive total calcium load (14, 15). This increased calcium load, combined with the previously mentioned hyperphosphatemia, may result in metastatic calcifications. Vascular calcifications are characteristically localized in the media of blood vessels, while atherosclerotic lesions are, contrastingly, localized in the intima. Medial calcification is an abnormality that produces stiffening of the arteries resulting in increased pulse pressure, increased pulse wave velocity, and increased systolic blood pressure. It is therefore important to monitor this and the other abnormalities that are found in the CKD population.

To further examine this issue, 49 Hispanic patients undergoing dialysis at the University Hospital dialysis unit were retrospectively evaluated for a 9-month period. The pertinent mineral and metabolic data were examined longitudinally to assess the efficiency of treatment so that changes intended to improve patient outcome could be implemented. It is important to stress that because the majority of the members of the study group were Hispanic, the results might not readily translate to a population composed primarily of non-Hispanics.

Methods

A retrospective review was performed on the charts of 49 stable patients who received ambulatory dialysis from November 2011 through June 2012 in the dialysis unit of the University Hospital. Measurements of serum phosphate, serum calcium (corrected to the albumin levels), intact PTH, and pulse pressure were made during 3 observations, taking place at 3-month intervals. Normal values for serum phosphate fall between 3.5 and 5.0 mg/dL; for corrected serum calcium, normal values

are between 8.8 and 9.5 mg/dL; for intact PTH, normal values are less than 65 pg/mL; and for pulse pressure, normal values are below 50 mmHg. The medications taken by each patient participating in this study were recorded. The medications evaluated were vitamin D analogs (paricalcitol and calcitriol), phosphate binders (calcium acetate and sevelamer), and a calcium-sensing receptor sensitizer (cinacalcet).

This study was approved by the Institutional Review Board (IRB) of the Medical Sciences Campus of the University of Puerto Rico.

Results

Table 1 shows the baseline characteristics of the population studied (n = 49). The age range was 23 to 87 years and the mean age was 67 years. There were 22 males and 27 females. Hypertension was present in 17 (35%) patients, and 14 (28%) had a history of diabetes. The average dialysis vintage was 2 years.

Table 2 depicts the time of observation in months and the average measurements of PTH, corrected serum calcium, and serum phosphate. Pulse pressure levels were calculated by subtracting the systolic from the diastolic blood pressure. In addition, the number of patients receiving each treatment is shown. The average measurements of serum PTH were elevated at each observation. At 3 months the average was 386 pg/mL, at 6 months, 358 pg/mL, and at 9 months, 384 pg/mL. The levels of serum calcium and serum phosphate were within normal ranges; however, pulse pressure was elevated at all observations. There was no observable difference between the use of calcium acetate versus sevelamer as a phosphate binder. Vitamin D analogs were used in almost 50% of the study population. In contrast, cinacalcet was rarely used.

Table 1. Baseline participant characteristics

Age	Range	23–87
	Mean	67
Sex	M	22 (45%)
	F	27 (55%)
Diabetes		14 (28%)
Hypertension		17 (35%)
Baseline PTH		625 pg/ml
Baseline calcium		10.1 mg/dL
Baseline phosphate		5.47 mg/dL
Dialysis vintage		2 years

Note: None of the patients had fractures, nor was BMD done before or during the observation period.

Table 2. Average measurements of serum PTH, calcium, phosphate, pulse pressure levels in all patients and the treatments received for the metabolic disorders.

Time of observation (months)	Intact PTH (pg/ml)	Serum calcium (corrected) (mg/dL)	Serum phosphate (mg/dL)	Pulse pressure (mmHg)	Calcium acetate	Sevelamer	Vitamin D (calcitriol or paricalcitol)	Cinacalcet
Baseline (3)	386	9.12	4.61	68	15	10	25	1
6	357	9.32	5.02	68	16	13	20	2
9	383	9.31	4.83	62	16	12	20	2

In Figure 1, an average PTH level of 625 pg/mL and a serum phosphate level of 5.47 were observed at 3 months. At 6 months, the average PTH level fell to 597 pg/mL, and the serum phosphate level to 5.45 pg/mL. At 9 months, we determined that the levels of both PTH and serum phosphate were higher than they had been in either of the previous 2 observational periods.
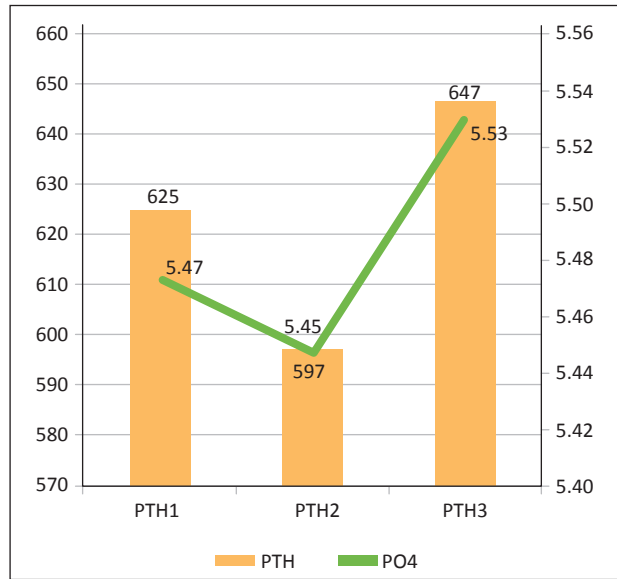
PTH	Coef	Std. Err.	t	P>t	(95% Conf. Interval)	
PO4	83.20518	34.93649	2.38	0.021	12.99768	153.4127
Cons	166.1731	197.3022	0.84	0.404	-230.3204	562.667

F(1,49)	Prob>F	R^2	Adj R^2	Root MSE
5.67	0.0212	0.1037	0.0855	338.21

As depicted in Figure 2, using linear regression analysis (Stata data analysis software), a statistically significant relationship ($p = 0.021$, $R^2 = 0.1037$, adjusted $R^2 = 0.0855$) was observed between the serum phosphate levels and the PTH levels. The predicted values for PTH follow a linear regression, indicating that PTH can be accurately predicted based on the PO4 level.

Pulse pressure measurements were obtained at each observation interval. Elevated pulse pressure was observed in 69% of the patients at 3 months, in 65% of the patients at 6 months, and in 57% of the patients at 9 months.

Figure 3 shows the relationship between calcium and pulse pressure in a subgroup of patients with elevated serum calcium. It can be observed that there is a trend toward an increase in pulse pressure as calcium levels rise above 9.5 mg/dL. Although this trend has been observed in this population, statistical tests do not support its validity in other populations.

Figure 1. Relationship between PTH and phosphate levels obtained during the 3 observations periods in a subgroup of the sample having PTH levels above 300 pg/ml (n = 16). An average PTH level of 625 pg/mL and a serum phosphate level of 5.47 were observed at 3 months. At 6 months, the average PTH level was reduced to 597 pg/mL, and the serum phosphate level was reduced to 5.45 pg/mL. At 9 months, an increase in PTH levels as well as in serum phosphate levels in comparison with the first 2 observations was observed.
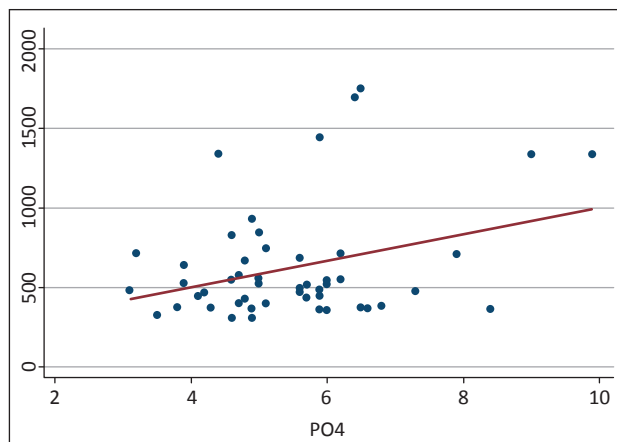

Figure 2. Linear regression between serum phosphate and PTH levels. Using a linear regression analysis, Stata data analysis software, a statistically significant relationship ($p = 0.021$, $R^2 = 0.1037$, adjusted $R^2 = 0.0855$) was observed between serum phosphate levels and PTH levels. The predicted values for PTH follow a linear regression, indicating that PTH can be accurately predicted based on PO4 level.

Figure 3. Relationship between pulse pressure and serum calcium corrected to the albumin concentration levels at each observation (n = 17). Shows the relationship between calcium and pulse pressure in a subgroup of patients with elevated serum calcium. It can be observed that there is a trend toward an increase in pulse pressure as calcium levels rise above 9.5 mg/dL. Although this trend has been observed in this population, statistical tests do not support its validity in other populations.
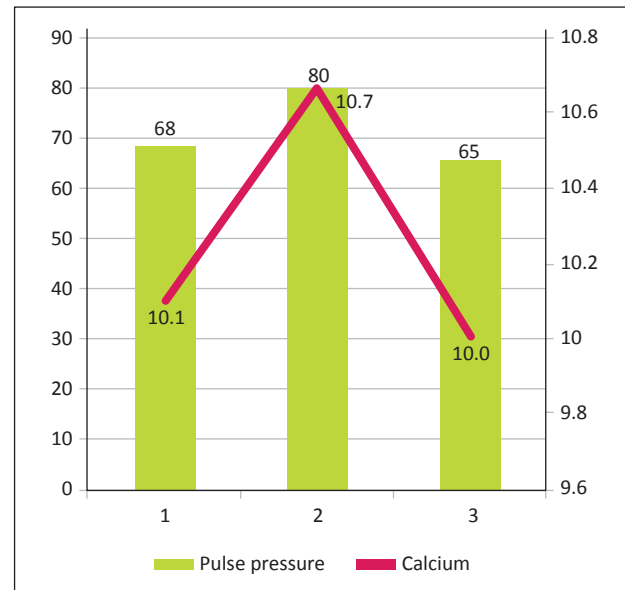
Discussion

Adequate phosphate control in CKD is formidably difficult, and efforts to reduce phosphate ingestion in the diet are rarely effective. Similarly, dialysis has been shown to have a limited ability to control phosphate levels. The use of phosphate binders, specifically calcium-based binders, have been associated with a "high" calcium balance, which has enhanced the precipitation of calcium in soft tissues, blood vessels, cardiac valves, and organs (14, 15). In addition the use of vitamin D analogs to decrease PTH may increase calcium levels and may indirectly perpetuate metastatic calcifications. In this group of patients, one third of the population was using calcium acetate binders and one half, vitamin D analogs. Despite this, the levels of calcium were not elevated except in 17 patients. Furthermore, only 2 patients were receiving cinacalcet, a calcimimetic agent, to decrease PTH and calcium levels. The introduction of sevelamer and lanthanum carbonate, 2 non-calcium binders, has been useful in reducing calcium levels in these patients. Both compounds may alleviate the development of soft tissue calcifications in CKD patients (16, 17). Animal and clinical studies have shown the salutary effects of sevelamer on both calcifications and the progression of renal impairment as well as on the attenuation of coronary calcifications in hemodialysis patients (12, 18, 19). In clinical practice the major barriers to placing CKD patients on non-calcium binders have been their high cost and the requirements some health insurers have with regard to these new phosphate binders. Therefore, it can be difficult for CKD patients to lower their calcium loads.

A recent randomized study of 114 incident hemodialysis patients ascertained (after an 18-month follow-up period) that taking sevelamer conferred a greater survival benefit than did taking calcium carbonate (20). On the other hand, a 4-year study comparing sevelamer to calcium binders did not show significant differences in all-cause or cardiovascular mortality. In this study, a subgroup of patients who were over 65 years of age and who were being treated with sevelamer were shown to experience significant effects (21).

Already extensively studied, vascular calcification is highly prevalent and occurs in even those patients who are under 30 years of age, an indication of its importance with regard to mortality (22, 23). In CKD stage 5, 80 to 85% of prevalent dialysis patients and 60% of incident patients have some degree of coronary or aortic (or both) calcification (24, 25). Calcifications in the vessels usually occur in 2 sites: the intima and the media. Intimal lesions occur as a consequence of inflammation, and calcifications of the vasculature's plaque are initiated early in life and may result in artery occlusion. Medial calcifications occur in the elastic lamina of large and medium vessels. They are seen in CKD patients. Medial calcification results in vascular stiffness, which is strongly associated with an increased mortality rate in the general population. Vascular calcifications contribute to left ventricular hypertrophy,

reducing coronary perfusion and promoting the development of cardiac arrhythmias and sudden death. In addition patients with CKD and severe vascular calcifications are more prone to non-traumatic bone fractures (26).

In our retrospective analysis, we found that pulse pressure, an indicator of arterial stiffness, was consistently elevated in our patients throughout the study period, which supports the indirect evidence of arterial stiffness. The mean age of our population was 67 years, and the dialysis vintage was 2 years, both of which time-related factors may be linked to arterial stiffness. On the other hand, the relationship between serum calcium and pulse pressure in a small group of patients was indicative of a trend toward a pulse-pressure increase as calcium levels escalated. A recent study in a cohort of 70 patients made a longitudinal assessment after 1 year with aortic pulse wave velocity measurements. The study found that over the course of 1 year, arterial stiffness increased (27).

The mechanisms involved in the production of vascular calcifications are complex. An elevated phosphorus level is a potent stimulus for the differentiation of vascular cells and osteoblast-like cells, which results in calcification of the media of vessels. The list of promoters and inhibitors of the calcification process is extensive and keeps increasing. The main interest has been placed on phosphorous, calcium, vitamin D, PTH, and lipids. Some other factors are recently drawing attention, such as osteoprotegerin, pyrophosphate, fetuin-A, and matrix GLA protein (28, 29, 30).

Measurements of vascular calcification and arterial stiffness by CT scan and pulse wave velocity are useful and recommendable non-invasive tools to ascertain cardiovascular disease in CKD. However, our study was retrospective and did not relate to any of the previously mentioned studies.

The limitations in our study are as follows: 1) it was a retrospective analysis, 2) a relatively small number of patients were studied, 3) there was no control group, and 4) no studies of arterial stiffness were made.

In conclusion, we herein report our experience in the management of patients on hemodialysis, which was focused on the goal of avoiding secondary hyperparathyroidism. The PTH levels of 33 of the 49 patients were fairly well controlled (under 300 pg/mL) over the course of the 9-month observation period. Sixteen patients demonstrated levels over 300 pg/mL, and a linear relationship was obtained with phosphate levels. These findings are crucial in trying to avoid mineral bone abnormalities in CKD patients on hemodialysis. We recommend that these patients receive close supervision of their phosphate and PTH levels and proper measures be taken to avoid increased morbidity and mortality. Moreover, a wide pulse pressure was observed in these patients, which did not improve during the 9 months of observation, denoting persistent elevated arterial stiffness, which is an additional major indicator of cardiovascular mortality in CKD patients.

Resumen

Un estudio retrospectivo se realizó de noviembre 2011 a junio 2012 en 49 pacientes estables en diálisis en la unidad de diálisis del Hospital Universitario. Se obtuvieron niveles de fosfato, calcio corregido a la albúmina, hormona paratiroidea (PTH) y presión de pulso a intervalos de 3 meses durante un periodo de observación de 9 meses. Estas observaciones longitudinales evaluaron la eficiencia de tratamiento con el propósito de hacer cambios para mejorar los resultados de estos pacientes. Treinta y tres de 49 pacientes demostraron control apropiado de los niveles de PTH. Dieciséis pacientes demostraron niveles sobre 300 pg/ml. Una relación lineal entre los niveles de PTH y los niveles de fosfato fue obtenida usando el análisis de Stata (p=0.021). El promedio de presión de pulso (PP) obtenidos en cada intervalo en 49 pacientes demostraron un aumento de la siguiente manera: 69% a 3 meses, 65% a 6 meses y 57% a 9 meses. Quelantes de fosfato que contienen calcio fueron usados en una tercera parte de la población de pacientes y análogos de vitamina D en 50%. La tendencia a un aumento en PP fue observada según los niveles de calcio aumentaban sobre 9.5 mg/dl. Se concluyó que estos pacientes necesitan una supervisión estrecha para evitar aumentos en la morbilidad y mortalidad asociada a disturbios del metabolismo mineral. Una PP amplia fue observada en estos pacientes durante 9 meses de observación demostrando una rigidez arterial que sugiere un descontrol en el balance de calcio.

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