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Increased serum phosphate concentrations in patients with advanced chronic kidney disease treated with diuretics

Francisco Caravaca, Guadalupe García-Pino, Rocío Martínez-Gallardo, Flavio Ferreira-Morong, Enrique Luna, Raúl Alvarado, Enrique Ruiz-Donoso, Edgar Chávez

Servicio de Nefrología. Hospital Infanta Cristina. Badajoz (Spain).

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ABSTRACT

Background: Serum phosphate concentrations usually show great variability in patients with advanced chronic kidney disease (CKD) not requiring dialysis. Diuretics can alter mineral metabolism, and according to previous clinical observations, they may increase serum phosphate levels. **Objectives:** This study aims to confirm whether diuretics are independently associated with increased serum phosphate concentrations, and to investigate by which mechanisms diuretics may affect phosphate metabolism. **Methods:** In this cross-sectional, single-centre study, 429 Caucasian patients with advanced CKD not on dialysis were included. In addition to conventional serum biochemical measures, the following parameters of renal phosphate excretion were assessed: 24 hours urinary phosphate excretion, tubular maximum phosphate reabsorption (TmP) per GFR, and fractional excretion of phosphate (FEP). **Results:** Fifty-eight percent of patients were on diuretics. Patients on diuretics showed significantly higher mean serum phosphate concentration (4.78±1.23 vs. 4.24±1.04mg/dl; p<.0001), and higher TmP per GFR (2.77±0.72 vs. 2.43±0.78mg/dl; p<.0001) than those of patients untreated with diuretics. By multivariate linear and logistic regression, significant associations between diuretics and serum phosphate concentrations or hyperphosphatemia remained after adjustment for potential confounding variables. In patients with the highest phosphate load weighted to kidney function, those treated with diuretics showed significantly lower FEP than that of patients untreated with diuretics. **Conclusions:** Diuretic treatment is associated with increased serum phosphate concentrations in patients with advanced CKD. Diuretics may indirectly interfere with the maximum renal compensatory capacity to excrete phosphate. Diuretics should be considered potential confounders in the relationship between serum phosphate concentrations and cardiovascular outcomes in patients with CKD.

Keywords: Diuretics. Fractional phosphorous excretion. Hyperphosphataemia. Chronic kidney disease.

Correspondence: Francisco Caravaca
Servicio de Nefrología.
Hospital Infanta Cristina. Badajoz. (Spain).
fcaravacam@senefro.org

Concentraciones más elevadas de fósforo sérico en pacientes con enfermedad renal crónica avanzada tratados con diuréticos

RESUMEN

Introducción: *Las concentraciones séricas de fósforo muestran una gran variabilidad en los pacientes con enfermedad renal crónica avanzada (ERCA) no en diálisis. El tratamiento con diuréticos puede influir en la severidad de las alteraciones óseo-minerales relacionadas con la ERCA, pero su efecto sobre los niveles de fósforo sérico es menos conocido.* ***Objetivos:*** *Determinar si existe una asociación independiente entre los niveles de fósforo sérico y el tratamiento con diuréticos, e investigar los mecanismos por los que los diuréticos podrían afectar el metabolismo del fósforo.* ***Material y métodos:*** *Estudio transversal en el que fueron incluidos 429 pacientes con ERCA. Además de las determinaciones analíticas convencionales, se incluyeron los siguientes parámetros: excreción urinaria de fósforo en 24 horas, reabsorción tubular máxima de fósforo (TmP) y fracción de excreción de fósforo (FEP).* ***Resultados:*** *El 55 % de los pacientes estaba en tratamiento con diuréticos. Con respecto a los no tratados con diuréticos, los que recibieron este tratamiento mostraron una concentración media de fósforo sérico significativamente superior (4,78 ± 1,23 vs. 4,24 ± 1,04 mg/dl; p < 0,0001), así como una mayor TmP (2,77 ± 0,72 vs. 2,43 ± 0,78 mg/dl; p < 0,0001). Por regresión lineal y logística múltiple, las asociaciones entre diuréticos y concentraciones de fósforo sérico o hiperfosfatemia (fósforo sérico > 4,5 mg/dl) mantuvieron las significaciones estadísticas tras ajuste con las principales variables confundentes. En los pacientes con la máxima carga de fósforo ajustada a función renal, aquellos tratados con diuréticos mostraron una FEP significativamente menor que los no tratados con diuréticos.* ***Conclusión:*** *El tratamiento con diuréticos en la ERCA se asocia a concentraciones más elevadas de fósforo sérico. Los diuréticos podrían interferir de forma indirecta con la máxima capacidad compensatoria renal de excretar fósforo. El tratamiento con diuréticos debería ser tenido en cuenta en los estudios que relacionan las concentraciones de fósforo sérico y las alteraciones cardiovasculares.*

Palabras clave: *Diuréticos. Fracción excreción fósforo. Hiperfosfatemia. Insuficiencia renal crónica.*

INTRODUCTION

The change in phosphate metabolism is an invariable consequence of chronic kidney disease (CKD). As the glomerular filtration rate (GFR) decreases, there is a requirement for a

compensatory increase in fractional excretion of phosphate, in order to maintain serum phosphate levels within the normal ranges. The dietary phosphate load, parathyroid hormone (PTH), and phosphatonins (fibroblast growth factor (FGF) 23, FGF-7, secreted frizzled-related protein 4, etc.) regulate renal excretion of phosphate by adjusting the expression of sodium-phosphate transporters (NaPi-IIa, NaPi-IIc, and type III PiT-2) in the apical membrane of proximal tubule cells.[1,2] This compensation mechanism is usually effective until the more advanced stages of renal failure. However, serum phosphate concentrations show great variability in patients with stages 3-5 predialysis CKD.[3,4] In addition to the severity of renal failure and the phosphate load, other factors may also favour the development of hyperphosphataemia, causing interference in the compensation mechanisms of renal excretion of phosphate.

Diuretics are used very frequently in CKD; these drugs may affect mineral metabolism, this being one of several adverse effects.[5,6] Furosemide increases renal calcium excretion and may aggravate secondary hyperparathyroidism in patients with CKD.[5,6] By contrast, thiazides reduce calciuria, although this effect appears to have very little impact on PTH levels.[6,7] However, there have been few studies on the effect of diuretics on phosphate metabolism in CKD.

In a previous study, we observed a higher prevalence of hyperphosphataemia in CKD patients treated with diuretics.[8] Another recent study also shows that moderate CKD patients treated with diuretics present significantly higher phosphate levels than patients not treated with diuretics.[6] Although this association appears to be independent of a number of potential confounding factors,[8] causality is still uncertain.

The objectives of this study were to confirm whether diuretics are independently associated with higher levels of serum phosphate in advanced predialysis CKD, and to investigate the mechanisms by which diuretics may affect phosphate metabolism.

MATERIAL AND METHOD

This cross-sectional study included 429 Caucasian patients (mean age 67±14 years, 201 were women). All patients were recruited consecutively in the Advanced Chronic Kidney Disease consultation during the period between June 2008 and December 2011 with the following inclusion criteria: age over 18, GFR under 40ml/min/1.73m^2, not having begun dialysis or being a kidney transplant patient, absence of acute intercurrent illness and severe changes in nutritional status. On extraction of samples for the study, no patient was being treated with phosphate binders or vitamin D.

Exclusion criteria were: treatment with corticosteroids and/or calcineurin inhibitors and patients with paraproteinaemia or multiple myeloma.

The information on the treatment that the patients were receiving was obtained by anamnesis and a review of medical records.

Laboratory methods

All samples for biochemical analysis were obtained from peripheral venous blood after an overnight fast. Patients were requested to bring the urine collected in the previous 24 hours on the day of sample extraction. The concentrations of phosphate, calcium, urea, creatinine and proteins in blood and urine were measured by conventional methods (Advia® Chemistry, Siemens Healthcare Diagnostics). The bicarbonate and plasma ionised calcium concentrations were measured by gasometry (ABL800 FLEX, Radiometer Ibérica). Also included in the study were serum albumin, uric acid, magnesium (colorimetric xylidyl blue) determinations and PTH levels (1-84 molecule, a chemiluminescent immunoassay, Diasorin).

Creatinine and urea clearances were measured and GFR was estimated as half the sum of these two clearances. GFR was also estimated by the MDRD equation with standardised creatinine values.[9]

The indirect estimation of protein intake was determined with the protein equivalent of non-protein nitrogen appearance (PNPNA), calculated by the combined Cottini et al. and Maroni et al. formulas, as described by Bergström et al.[10]

Phosphate excretion was calculated in the 24-hour urine samples and was presented as total and normalised excretion to the GFR measured (milligrams of phosphate excreted in 24 hours per ml/min/1.73m^2 of GFR). The latter parameter aims to estimate the daily phosphate load of the patient normalised to their renal function.

The calcium excretion rate was calculated according the formula: urine calcium x plasma creatinine/urine creatinine

Tubular maximum phosphate reabsorption by GFR was calculated using the following formula: plasma phosphate - (urine phosphate/urine creatinine) x blood creatinine.

Fractional excretion of phosphate, expressed as a percentage, was calculated using the formula: (urine phosphate x plasma creatinine x 100)/(plasma phosphate x urine creatinine).

Study design and statistical methods

Transversal study comparing serum phosphate concentrations and phosphate renal excretion in patients treated or not with diuretics. The independent association

between treatment with diuretics and phosphate levels or hyperphosphataemia (serum phosphate>4.5mg/dl) was also analysed by linear and multiple logistic regression.

In order to establish the maximum compensatory renal capacity to excrete phosphate, the fractional excretion of phosphate was correlated with the phosphate load normalised to kidney function.

To estimate the size of the sample, the following assumptions were made: Type I error (alpha) of 0.05; power of the study 80%; clinically significant difference of serum phosphate concentrations between subgroups of 0.40 mg/dl; and standard deviation of serum phosphate concentrations of 1.1mg/dl. Thus, the minimum number of patients that should be included patients was estimated at 424.

To compare continuous variables in patients treated or not with diuretics, the Student *t* test or the Mann-Whitney test were used, depending on the characteristics of the variable distribution. The χ^2 test was used to compare categorical variables between subgroups.

The discrimination power of total phosphate excretion normalised to GFR to associate with hyperphosphataemia was analysed by ROC (receiver operating characteristic) curves.

To establish the independent association of diuretic treatment with serum phosphate levels or hyperphosphataemia, we used multiple linear and logistic regression, respectively. Independent variables included in these models were: age, sex, GFR, phosphate load, diabetes, serum albumin, serum bicarbonate, proteinuria, PTH and estimated protein intake (PNPNA). For the selection of covariates with better predictive models, the automatic process of conditional progressive elimination was used (backward).

Data were presented as mean ± standard deviation. A *p* less than .05 was considered as statistically significant. For statistical analysis and producing graphs, the SPSS software version 15.0 (SPSS, Chicago, USA) and STATA version 11.1 (Stata Corporation, Texas, USA) were used.

RESULTS

Differences between patients with and without diuretics

The percentage of patients treated with diuretics was 58%. Table 1 shows the demographic, clinical and biochemical characteristics of the total group and the two subgroups according to whether or not they were treated with diuretics.

A higher percentage of patients treated with diuretics had diabetes mellitus, a history of heart failure, ischaemic heart disease and peripheral ischemia. Patients with diuretics showed higher proteinuria and lower concentrations of serum albumin than those not treated with diuretics. There were no significant differences regarding age, sex or GFR.

Patients treated with diuretics showed a mean concentration of serum phosphate significantly higher than those not treated with diuretics (4.78±1.23 vs. 4.24±1.04 mg/dl, 95% confidence interval of the difference = 0.76 and 0.32mg/dl, $p<.0001$).

Tubular maximum phosphate reabsorption was also significantly higher in patients treated with diuretics, although the total urine phosphate excretion and fractional excretion of phosphate showed no significant differences between subgroups treated and those not treated with diuretics (Table 1).

Patients treated with diuretics showed lower levels of total and ionised calcium, although the differences in the PTH and urinary calcium excretion levels were not significant (Table 1).

The type of diuretic most used was furosemide (151 patients), followed by torasemide (68 patients) and thiazides (23 patients). Serum phosphate levels in each subgroup by type of diuretic were significantly higher than those in the subgroup without diuretics: the furosemide subgroup (serum phosphate 4.80±1.28mg/dl, $p=.001$); the torasemide subgroup (serum phosphate = 4.72±1.19mg/dl, $p<.05$), and the thiazides subgroup (serum phosphate = 4.96±1.11mg/dl, $p<.05$).

The tubular maximum phosphate reabsorption was also significantly higher in each of the subgroups treated with diuretics with respect to those not treated. No significant differences were found between subgroups in the rest of the parameters studied.

Determinants of serum phosphate levels and hyperphosphataemia

Hyperphosphataemia (serum phosphate> 4.5mg/dl) was observed in 183 patients (43%).

In univariate linear regression analysis, serum phosphate levels were correlated with GFR ($R^2=0.360$, $p<.0001$) and total urinary excretion of phosphate ($R^2=0.040$, $p<.0001$). However, the interaction of these two parameters, that is, the load of phosphate normalised to GFR, substantially improved the correlation with serum phosphate concentrations ($R^2=0.620$) (Figure 1).

Table 1. Demographic, clinical and biochemical characteristics of the total study group and the subgroups according to treatment or no treatment with diuretics

	Total n = 429	With diuretics n = 247	Without diuretics n = 182	P[a]
Age, years	67±14	68±13	66±16	0.285
Sex male, %	53	53	54	0.803
Diabetes, %	31	40	20	<0.0001
History of heart failure, %	12	19	3	<0.0001
History of coronary ischaemia, %	14	19	8	0.001
History of cerebrovascular ischaemia, %	10	12	8	0.133
History of peripheral vascular disease, %	6	8	3	0.039
Glomerular filtration rate-MDRD, ml/min/1.73m^2	14.7±5.9	14.4±5.6	15.2±6.3	0.139
Glomerular filtration rate, (Ccr+Cu)/2, ml/min/1.73 m^2	12.5±5.1	12.1±4.8	13.1±5.5	0.037
Proteinuria, mg/g creatinine	2259±2545	2551±2873	1863±1954	0.006
Serum albumin, g/dl	4.01±0.43	3.94±0.56	4.05±0.41	0.022
PNPNA, g/kg/day	0.81±0.27	0.81±0.26	0.82±0.28	0.617
Serum urate, mg/dl	7.46±1.99	7.59±2.14	7.27±1.76	0.090
Serum phosphate, mg/dl	4.55±1.18	4.78±1.23	4.24±1.04	<0.0001
Total serum calcium, mg/dl	9.18±0.79	9.11±0.79	9.29±0.77	0.014
Ionic calcium, mmol/l	1.22±0.09	1.21±0.10	1.23±0.09	0.014
Serum magnesium, mg/dl	2.05±0.33	2.07±0.36	2.01±0.38	0.082
Serum bicarbonate, mmol/l	21.8±3.7	21.7±3.7	21.9±3.7	0.447
PTH, pg/ml	337±234	352±236	315±229	0.111
Urinary excretion of calcium, mg/24 h	37±30	36±28	39±31	0.319
Rate of urinary excretion of calcium, mg/dl	0.158±0.153	0.153±0.139	0.165±0.170	0.399
Urinary phosphate excretion, mg/24 h	468±195	484±197	446±190	0.053
Tubular maximum phosphate reabsorption /GFR, mg/dl	2.63±0.76	2.77±0.72	2.43±0.78	<0.0001
Fractional excretion of phosphate, %	41.8±10.8	41.3±9.7	42.4±12.1	0.321

[a] Statistical significance of the results between patients treated and not treated with diuretics.
GFR: glomerular filtration rate; PNPNA: protein equivalent of non-protein nitrogen appearance; PTH: parathyroid hormone, Ccr: creatinine clearance rate; Cu: urea clearance rate.

Serum phosphate levels were also correlated positively with proteinuria (R^2=0.126, p<.0001) and negatively with serum albumin concentrations (R^2=0.034, p<.0001).

Using multiple linear regression (Table 2), the phosphate load normalized to the GFR was the best determining factor of levels of serum phosphate (beta=0.721), followed by age, sex, serum albumin, serum bicarbonate and treatment with diuretics.

By multiple logistic regression (Table 3), treatment with diuretics was also independently associated with hyperphosphataemia (odds ratio=1.917, p=.019).

In the ROC curve analysis, the phosphate load normalised to GFR was significantly associated with hyperphosphataemia (area under the curve=.861, p<.0001). A value of 40mg of daily urinary excretion per ml/min/1.73 m^2 of GFR marked the cut-off point for hyperphosphataemia, with a sensitivity and specificity, both of 75%.

Differences in fractional excretion of phosphate in patients treated and not treated with diuretics

Figure 2 shows curves that best fit the correlation between fractional excretion of the phosphate and GFR-normalised phosphate load in both subgroups. The two curves were virtually identical in the lower section of phosphate load. However, in patients with phosphate overload, the maximum compensatory capacity to excrete phosphate, represented by the maximum fractional excretion of phosphate, reached higher levels in patients not treated with diuretics.

A separate analysis of the data for patients with higher phosphate load normalised to GFR (Table 4) showed that both serum phosphate levels and maximum tubular

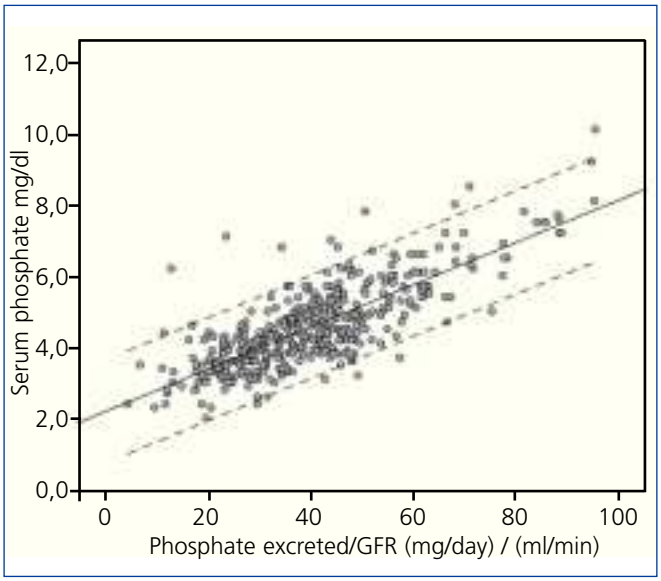

Figure 1. Correlation between levels of serum phosphate and phosphate load normalised to the glomerular filtration rate.
R^2 =0.620; p<.0001. The broken lines show 95% confidence intervals. GFR: glomerular filtration rate.

reabsorption of phosphate were significantly higher in patients treated with diuretics, while the fractional excretion of phosphate was significantly higher in patients not treated with diuretics.

The expected correlation between PTH levels and fractional excretion of phosphate also showed differences in accordance with diuretic treatment (Figure 3).

The association between the excretion of phosphate and sodium in 24 hr. urine in a subgroup of 160 patients in which these two parameters were determined, showed an interesting divergence from natriuresis values of 50mmol/24h (Figure 4). In the same sodium excretion, patients with diuretics excreted less phosphate than those not treated with this drug.

DISCUSSION

The results of this study show that CKD patients treated with diuretics have higher phosphate concentrations than untreated patients. The significant association between diuretic treatment and hyperphosphataemia persisted after adjusting results based on variables that could potentially confound this association. Patients treated with diuretics showed a higher maximum phosphate reabsorption and in situations of higher phosphate load, the patients treated with diuretics showed a fractional excretion of phosphate significantly lower than those untreated.

Although this study cannot prove a causal relationship between the diuretic treatment and high levels of serum phosphate due to the cross-sectional design, these findings suggest that diuretics may directly or indirectly interfere with compensatory mechanisms of renal excretion of phosphate in CKD.

In this study, several parameters are used for renal excretion of phosphate which merit comment for a better understanding of the results. Briefly, the relationship between total urinary phosphate excretion and the measurement of kidney function (GFR), a parameter known as the 'the phosphate load normalised to GFR' was the best determining factor of serum phosphate levels in the study population. Urinary excretion of phosphate above 40mg per ml/min/1.73 m^2 of GFR (e.g., 400mg of urinary excretion of phosphate in patients with a GFR of 10ml/min or 800mg in patients with 20ml/min of GFR) was the best determining factor of hyperphosphataemia. These findings fully correspond to the pathophysiology of CKD mineral alterations.

The compensatory renal excretion of phosphate, represented as a fraction of phosphate excretion, increases almost linearly as the phosphate load normalised to GFR increases, but up to a maximum level that corresponds approximately to the cut-off point where hyperphosphataemia begins to be observed. This fractional maximum excretion of phosphate

Table 2. Multiple linear regression on determining factors of serum phosphate concentrations[a]

Independent variable	Beta	R partial	P
Phosphate load/glomerular filtration rate	0.727	0.751	<0.0001
Sex (male = 1)	-0.161	-0.271	<0.0001
Age	-0.080	-0.133	0.007
Serum bicarbonate	-0.127	-0.202	<0.0001
Serum albumin	-0.144	-0.243	<0.0001
Treatment with diuretics	0.062	0.108	0.029

[a] Multiple R=0.830; R^2=0.689.

Table 3. Multiple logistic regression on determining factors of hyperphosphataemia (serum phosphate > 4.5mg/dl)

Independent variable	Odds ratio	95% CI odds ratio	*P*
Sex (male = 1)	0.310	0.175-0.552	<0.0001
Phosphate load/glomerular filtration rate, mg/24 h per ml/min/1.73 m^2	1.152	1.117-1.890	<0.0001
Serum bicarbonate, mmol/l	0.795	0.705-0.897	<0.0001
PNPNA, g/kg/day	2.878	1.072-7.727	0.036
Diuretic treatment (0.1)	1.917	1.113-3.304	0.019

CI: confidence interval; PNPNA: protein equivalent of non-protein nitrogen appearance (protein catabolic rate).
Outside the best predictive equation: age, serum albumin, proteinuria, diabetes and parathyroid hormone.

was significantly higher in patients not treated with diuretics than in those treated with this medication. This finding may help explain the differences in serum phosphate levels between subgroups.

Diuretics may affect mineral metabolism.[5,6] While furosemide increases renal calcium excretion, thiazides increase tubular calcium reabsorption, mainly through a mechanism coupled with tubular sodium reabsorption in response to reduced extracellular fluid volume.[11] Thus, the type of diuretic used in CKD patients may influence the calcium balance and the severity of secondary hyperparathyroidism.[5,6] However, there have been few studies on the effect of diuretics on serum phosphate levels in patients with CKD.

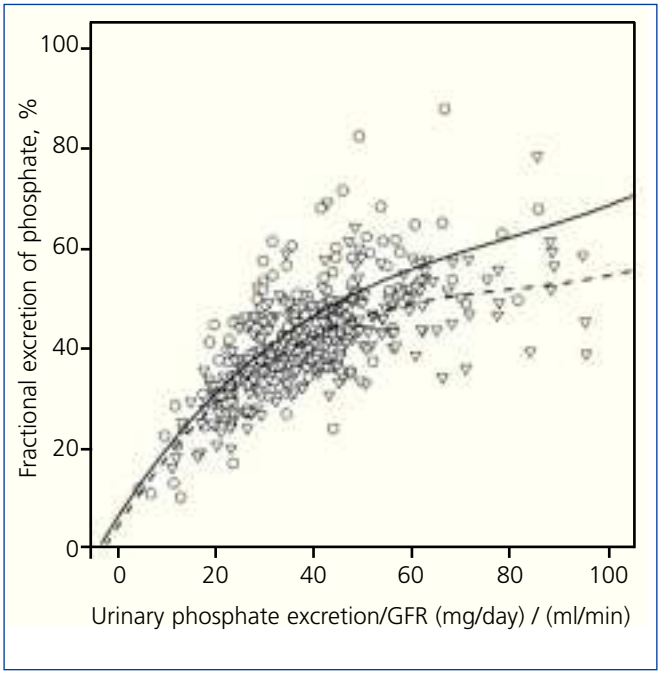

Figure 2. Correlation between fractional excretion of phosphate and phosphate load normalised to the glomerular filtration rate.
The white circles and the unbroken curve represent patients not treated with diuretics (R^2=0.533; p<.0001), while the inverted triangles and the broken curve represent patients treated with diuretics (R^2=0.517; p<.0001).
GFR: glomerular filtration rate.

A direct inhibitory effect of a diuretic on phosphate reabsorption in the proximal tubule has only been described with acetazolamide, a carbonic anhydrase inhibitor.[12] The effect of other diuretics on phosphate reabsorption in the proximal tubule largely correlates with its ability as a carbonic anhydrase inhibitor.[12] However, there has been no stimulant pharmacological effect of diuretics on tubular transport of phosphate, and therefore, it seems very unlikely that a direct effect of diuretics on phosphate metabolism can explain our findings.

Thiazides have been successfully employed to increase levels of serum phosphate in hypophosphatemic rickets,[13] a disease characterised by urinary phosphate loss. The basis for the success of this treatment seems to be related to changes in extracellular volume. The expansion of extracellular fluid decreases tubular phosphate reabsorption.[14] By contrast, extracellular volume contraction induced by thiazides may increase tubular phosphate reabsorption.[1,2,13] Although in this study we did not measure extracellular volume of patients, some possible mechanisms to explain these findings could be related to the reduction of extracellular volume or effective circulating volume, coupled with changes in tubular sodium and phosphate reabsorption.

Each of the three types of diuretics (furosemide, thiazides and torasemide) used in this study were associated with a significantly higher mean phosphate concentration than that of patients not treated with diuretics. This finding suggests the absence of pharmacological specificity in the hyperphosphataemic effect of diuretics.

In the present study, serum phosphate concentrations correlated positively with proteinuria and negatively with serum albumin. In the multiple linear regression analysis,

Table 4. Clinical and biochemical characteristics of the patients with increased levels of phosphate load adjusted to the glomerular filtration rate (> 40mg/day per ml/min/1.73m²)

	With diuretics n = 135	Without diuretics n = 64	*P*
Age, years	64±13	63±14	0.45
Sex, male %	64	61	0.803
Diabetes, %	43	19	0.001
Glomerular filtration rate (MDRD), ml/min/1.73 m²	11.9±4.0	11.9±4.4	0.925
Proteinuria, mg/g creatinine	3229±3339	2182±1945	0.021
Serum albumin, g/dl	3.92±0.61	4.10±0.41	0.032
PNPNA, g/kg/day	0.81±0.26	0.82±0.26	0.683
Serum urate, mg/dl	7.59±2.13	7.46±1.91	0.672
Serum phosphate, mg/dl	5.47±1.16	4.91±1.06	0.001
Total serum calcium, mg/dl	8.93±0.93	9.11±0.94	0.205
Ionic calcium, mmol/l	1.22±0.10	1.19±0.12	0.087
Serum magnesium, mg/dl	2.11±0.38	2.01±0.45	0.113
Sodium bicarbonate, mmol/l	20.7±3.6	20.3±3.5	0.512
PTH, pg/ml	430±248	406±282	0.544
Urinary phosphate excretion, mg/24 h	561±200	558±192	0.937
Tmax phosphate	2.94±0.77	2.43±0.86	<0.0001
Fractional excretion of phosphate, %	46.4±7.8	51,1±11.0	0.001

PNPNA: protein equivalent of non-protein nitrogen appearance (protein catabolic rate); PTH: parathyroid hormone.
[a] Maximum tubular phosphate reabsorption adjusted to the glomerular filtration rate.

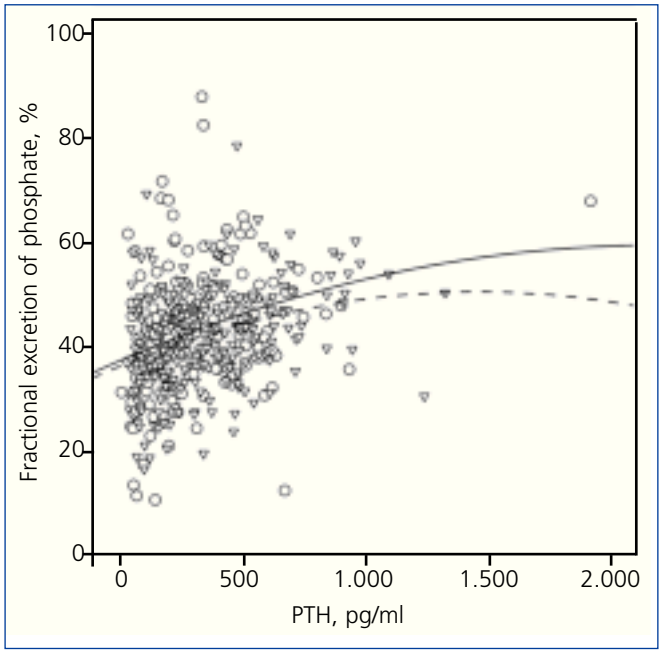

Figure 3. Correlation between fractional excretion of phosphate and serum concentrations of the parathyroid hormone.
The white circles and the unbroken curve represent patients not treated with diuretics (R^2=0.085; p<.0001), while the inverted triangles and the broken curve represent patients treated with diuretics (R^2=0.105; p<.0001).
PTH: parathyroid hormone.

serum albumin and diuretic treatment maintained significance as predictive variables of phosphate concentrations, but not proteinuria. Other studies have also found this interesting relationship between proteinuria and phosphate levels in blood,[15-18] although none provide information on the use of diuretics.

Phosphate has been recognised as a new cardiovascular risk factor and in CKD patients not on dialysis, hyperphosphataemia is associated with increased mortality.[4,19] Since the use of diuretics is associated most often with a high cardiovascular risk profile, and while these drugs may increase the levels of serum phosphate, the inclusion of diuretic treatment as a potential confounding factor may help better define the role of phosphate and perhaps of phosphatonins, in the development of cardiovascular complications in the general population and especially in CKD.

This study has several limitations. The cross-sectional design prevents causality and temporality of this association from being established unequivocally. This study was carried out at one single centre, the participants were all Caucasian and most were elderly. Levels of 25-hydroxy-vitamin D, 1,25-dihydroxyvitamin D, FGF-23 or other phosphatonins were not measured. Eight patients (six of them not treated with diuretics) showed a very high fractional excretion of phosphate (>65%), probably related to proximal tubular dysfunction. However,

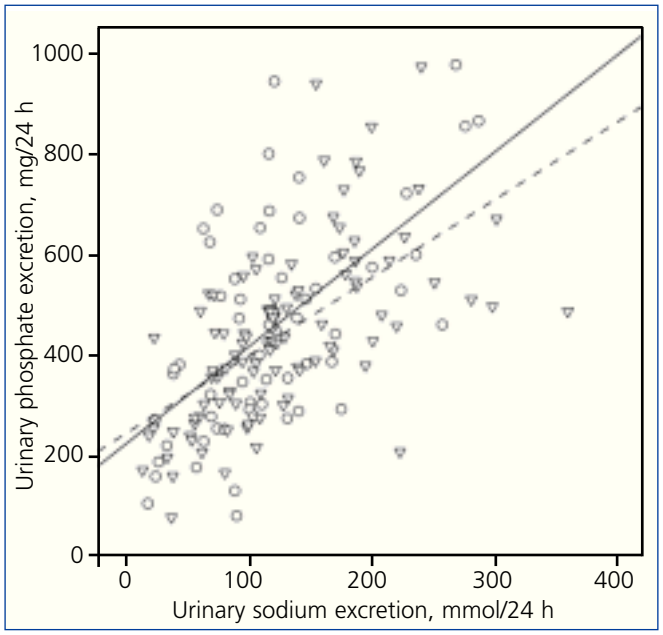

Figure 4. Correlation between urinary phosphate and sodium excretion over 24 hours.
The white circles and the unbroken curve represent patients not treated with diuretics (R^2=0,351; p<.0001), while the inverted triangles and the broken curve represent patients treated with diuretics (R^2=0.368; p<.0001).

exclusion of these patients did not substantially change the results or the statistical significance of the differences found between patients treated and not treated with diuretics.

In conclusion, treatment with diuretics in advanced CKD is associated with higher serum phosphate concentrations. Diuretics may interfere indirectly with the maximum compensatory capacity of the kidney to excrete phosphate. Diuretics treatment should be considered in studies linking serum phosphate concentrations and cardiovascular changes.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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