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Phosphocalcic Profile of Chronic Kidney Disease at Libreville

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: As kidney function declines towards the more severe stages of chronic kidney disease (CKD), the interactions between kidney, intestine and bone become increasingly unstable. CKD with mineral and bone disorders and secondary hyperparathyroidism would be developing. The aim of this study was to determine the phosphocalcic profile of CKD patients in Libreville.
Materials and Methods: This was a cross sectional study with 89 CKD patients recruited. A blood sample was taken to measure PTH, vitamin D, FGF-23 by ELISA method; calcium, magnesium, fasting blood glucose, phosphate and creatinine by spectrophotometer.
Results: Mean phosphorus levels were 1.3 ± 0.5 mmol/L and hormone levels 81.8 ± 26.2 pg/mL and 27.5 ± 5.0 ng/mL for PTH and vitamin D respectively. Significant hyperphosphatemia was found among 43 (48.3%; p=0.0135) patients. There were 59 (66.3%) subjects with hypovitaminosis D

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p=0.0000. Less than 50% of patients had normal blood glucose levels (p=0.0034). PTH was 99.4 ± 16.4 pg/mL in dialysis patients and 61.7 ± 20.3 pg/mL in non-dialysis patients, with a p=0.0000. Vitamin D levels were significantly higher in patients without calcium supplementation (29.5 ± 5.0 ng/mL) than in those with supplementation (25.1 ± 4.0 ng/mL, p= 0.0000).

Conclusion: Phosphate levels remained high in our study population. Vitamin D deficiency was found in the majority of our patients. It would be advisable to readjust the management of these patients in order to minimize the effects of hyperphosphatemia and improve life quality.

Keywords: Hyperphosphatemia; mineral; vitamin D; hormones.

1. INTRODUCTION

Chronic kidney disease (CKD) is defined as an abnormality of renal structure or function, present for more than 3 months [1]. It is characterized by a glomerular filtration rate (GFR) of less than 60 ml/minute/1.73m2 [1-2]. Epidemiological studies conducted worldwide estimated a general population prevalence of 10-15% [2-3]. More specifically, in adults, it represents 15-20% worldwide. In Africa, the true prevalence of this disease is unknown, and the associated clinical and genetic risk factors remain under-researched [4]. In Gabon, the extent of CKD remains poorly understood. However, the vital prognosis of patients suffering from CKD is affected. Calcium and phosphorus homeostasis are maintained by interactions between the kidneys, the intestine and the bones. They are mediated by several hormones, notably vitamin D, parathyroid hormone (PTH) and Fibroblast Growth Factor 23 (FGF-23). Phosphorus is involved in a number of biological functions, including skeletal bone stability, energy metabolism in all cells, DNA synthesis and intracellular signaling cascades. It is mainly found in diet and 90% of this mineral is stored in the skeleton as hydroxyapatite, 9% in soft tissues and 1% in the extracellular sector [1-3]. The kidney is the main organ controlling inorganic phosphate concentration [5]. Physiologically, inorganic phosphate stimulates PTH secretion in the parathyroid gland, which in turn stimulates renal calcitriol synthesis and, indirectly, intestinal absorption of inorganic phosphate. FGF-23, a phosphate-regulating hormone involved in bone mineral metabolism, stimulates excretion of inorganic phosphate in the kidneys [6-7]. As kidney function declines towards the more severe stages of chronic kidney disease (CKD), the interactions between kidney, intestine and bone become increasingly unstable. CKD with mineral and bone disorders would lead to a secondary hyperparathyroidism [8]. Similarly, hyperphosphatemia, defined as a serum phosphate level above 4.5 mg/dL (1.46 mmol/L), is a late complication of CKD [9]. This leads to cardiovascular damage characterized by vascular calcifications with cardiac repercussions. Consequently, these cardiovascular complications are the cause of increased morbidity and mortality in people with chronic kidney failure. [1,3,10]. In view of this, the aim of this study was to determine the phosphocalcic profile of CKD patients in Libreville, in order to help improve the management of these patients.

2. MATERIALS AND METHODS

2.1 Study Site

This was a 3-month cross-sectional study, which ran from 1st December 2022 to 28th February 2023.Patients were recruited at the *Centre National d'Hemodialyse (CNH)* of *the Centre Hospitalier Universitaire de Libreville (CHUL)*. Biological assays were performed at the Biochemistry Laboratory of the University of Health Sciences and at the National Public Health Laboratory in Libreville.

2.2 Study Population

Patients included were chronic kidney disease stage 3-5 on dialysis or not. There was no gender distinction, and age was greater than or equal to 15 years. They were included after giving their informed consent after explanation the study aim. Pregnant and breast-feeding women were excluded from the study.

Socio-clinical data were collected. A blood sample was taken to measure PTH, vitamin D, FGF-23, blood calcium, blood magnesium, fasting blood glucose, blood phosphate and serum creatinine. A 24-hour urine sample was taken for phosphate determination.

2.3 Biological Assays

2.3.1 Determination of minerals, blood sugar and renal function parameters

Calcemia, phosphatemia, magnesemia, glycemia, creatinemia and phosphaturia were

determined spectrophotometrically using standard methods [11-14]. Glomerular filtration rate was determined according to CKD-EPI (chronic kidney disease epidemiology collaboration) [15].

2.3.2 Hormones assays

Plasma assays for vitamin D, FGF-23 and PTH were performed by ELISA using kits recommended by the manufacturer.

2.4 Statistical Analysis

Data were collected on a survey form, then transferred to a Microsoft office® 2013 Excel file. Statistical analysis was performed using CDC's Epi info TM 7.2.0.1 software. Proportions, means and standard deviations were calculated. The Chi2 test was used to compare proportions. Relationships between qualitative and quantitative variables were studied using the Pearson test. The difference was statistically significant when the P value was less than 0.05.

3. RESULTS

The mean age of the population was 54.5 ± 15.8 years, with a systolic blood pressure of 148 ± 21.0 mmHg. People aged 40-59 were more affected by chronic kidney failure. However, in the under-40s, 16.9% had CKD (Table 1). Furthermore, the study population comprised 52 (58.4%) men and 37 (41.6%) women p=0.0355. There were more hypertensive (83.1%; p=0.0000) followed by diabetics. In this sample, 77 (86.5%) patients were on iron supplementation, 39 (43.8%) were on calcium supplementation and 24 (27.0%) were on furosemide. Of the 89 patients, 43 (48.3%) were on dialysis. In regard to diet, 14.6% consumed alcohol and 62.9% meat. Fish, fruit and vegetables were consumed by almost the entire population frequently (Table 1).

In the study population, mean phosphorus levels were 1.3 ± 0.5 mmol/L, with extremes ranging from 0.4 to 3.0 mmol/L. Mean hormone levels were 81.8 ± 26.2 pg/mL and 27.5 ± 5.0 ng/mL for serum PTH (extremes ranging from 23.4 to 120.2 pg/mL) and serum vitamin D (extremes ranging from 20.1 to 39.4 ng/mL) respectively. Mean glomerular filtration rate was 15.7 ± 12.8 mL/min/1.73 m^2 , with extremes ranging from 2.4 to 53.3 mL/min/1.73 m^2 (Table 2). In terms of frequency, 43 (48.3%; p=0.0135) had significant hyperphosphatemia. In addition, 40 (45.5%; p=0.1771) patients had elevated FGF-23 levels. There were 59 (66.3%) subjects with hypovitaminosis D p=0.0000. PTH levels were elevated in 61 (68.5%; p=0.0000) subjects. Less than 50% of patients had normal blood glucose levels (p=0.0034) (Table 2).

Serum phosphorus levels were 1.4 ±0.4 in women and 1.3 ±0.5 in men (p=0.7018). Mean serum calcium was comparable in both sexes (p=0.8459). Serum FGF-23 was 53.0 ± 20.1 ng/ml in women and 58.8 ± 25.3 in men (p=0.2528) Table 3.

Serum PTH was 99.4 ± 16.4 pg/mL in dialysis patients and 61.7 ± 20.3 pg/mL in non-dialysis patients, with a p=0.0000 value. Similarly, serum vitamin D levels were significantly higher in non-dialysis patients (31.2 ± 4.1 ng/mL) than in dialysis patients (24.3 ± 3.1 ng/mL), with a p=0.0000 value. Serum magnesium levels were comparable in dialysis and non-dialysis patients (p=0.2648). A mean serum calcium level of 2.2 ± 0.2 mmol/L was found in dialysis subjects and 2.4 ± 0.1 mmol/L in non-dialysis subjects, with a p=0.0005 value (Table 3).

Serum vitamin D levels were significantly higher in subjects taking furosemide 30.0 ± 5.6 ng/mL compared with those not taking furosemide 26.7 ± 4.5 ng/mL for a value of p=0.0039. Serum PTH was significantly higher in patients not taking furosemide 87.1 ± 23.7 mmol/L compared with those taking furosemide 67.7 ± 27.7 pg/mL for a value of p=0.0015 Table 3.

Mean serum calcium levels in calcium-supplemented and non-supplemented patients were comparable (p= 0.0609). Serum vitamin D levels were significantly higher in patients without calcium supplementation (29.5 ± 5.0 ng/mL) than in those with supplementation (25.1 ± 4.0 ng/mL, p= 0.0000). Nevertheless, serum PTH levels were 96.0 ± 19.3 pg/mL in the supplemented subjects and 70.7 ± 25.8 pg/mL in the non-supplemented subjects (p= 0.0000) (Table 3).

Table 1. Characteristic of the study population

Parameters	Mean (±SD)	P value
Age (years)	54.5 (±15.8)	NA
DBP (mmHg)	89.1 (±14.7)	NA
SBP(mmHg)	148 (±21.0)	NA
Weight (kg)	72.7 (±17.3)	NA
BMI (kg/m^2)	26.1 (±5.4)	NA
	Frequency n (%)	
CKD according to age (years)		
<40	15 (16.9)	
40-59	37 (41.6)	
60-74	27 (30.3)	0.1595
≥75	10 (11.2)	
Sex		
Men	52 (58.4)	0.0355
Women	37 (41.6)	
Comorbidities		
Type 2 diabetes	33 (37.1)	
High blood pressure	74 (82.0)	0.0000
HIV	12 (13.5)	
Treatment		
Iron	77 (86.5)	
Calcium	39 (43.8)	0.0000
Furosemide	24 (27.0)	
Dialysis	43 (48.3)	
CKD stage		
3	13 (14.6)	
4	30 (33.7)	0.0227
5	46 (51.7)	
Alcohol consumption	13 (14.6)	0.0000
Tobacco	01 (1.1)	0.0000
Diaries		
Fish	87 (97.8)	
Meat	56 (62.9)	0.0000
Vegetables	88 (98.9)	
Fruits	85 (95.5)	
Beverages	89 (100%)	

Table 2. Mean and proportion of biological parameters

Parameters	Mean (± SD)	Frequency n (%)	P value
Phosphoremia (mmol/L)	1.3 (± 0.5)		
High		43(48.3)	
Low		20(22.5)	0.0135
Normal		26(29.2)	
Calcemia (mmol/L)	2.3 (± 0.2)		
High		2(2.3)	
Low		5(5.6)	0.0000
Normal		82(92.1)	
Magnesemia (mmol/L)	0.9 (± 0.1)		
High		10(11.2)	0.0000
Normal		79(88.8)	
PTH (pg/mL)	81.8 (±26.2)		
High		61 (68.5)	0.0000
Normal		28 (31.5)	
Vitamin D (ng/mL)	27.5 (± 5.0)		
High		59 (66.3)	0.0000
Normal		30 (33.7)	
FGF-23 (pg/mL)	56.4 (± 23.3)		
High		40 (45.5)	
Low		9 (10.2)	0.1771
Normal		39 (44.3)	
Phosphaturia (mmol/L)	8.9 (± 9.2)		
Low		65 (82.3)	0.0000
Normal		14 (17.7)	
Creatininemia (µmol/L)	658.3 (± 460.7)		
High		88 (98.9)	0.0000
Normal		01 (1.1)	

Parameters	Mean (± SD)	Frequency n (%)	P value
GFR (mL/min)	15.7 (± 12.8)		
Low		89 (100)	0.0000
Glycemia (mmol/L)	5.6 (± 2.2)		
High		25 (28.1)	0.0034
Low		19 (21.3)	
Normal		45 (50.6)	

GFR : Glomerular filtration rate

4. DISCUSSION

In this study, the average age of the patients was 54.5 ±15.8 years, with extremes ranging from 18 to 89 years, and they were predominantly male. The young age of 18 indicates a serious situation. This suggests the need for earlier preventive measures to raise awareness of hypertension and diabetes, as these two parameters were the most common contributors to the onset of CKD. These results are similar to those of Ramilitiana and colleagues, in 2016 [16]. This male predominance may be explained by the fact that women are less likely to develop CKD and reach end-stage renal failure than men, as the decline in renal function is slower in women [17].

The deterioration in renal function will have an impact on the majority of minerals, due to their excretion from the body, mainly via the urine. Nevertheless, serum magnesium levels were normal in the majority of patients (88.8%). This could be explained on the one hand by fractional excretion of magnesium to compensate for reduced dietary intake, and on the other by preserved transcellular intestinal absorption. The magnesium concentration of the dialysate could also be considered. In addition, starchy foods and magnesium-rich vegetables were consumed by almost 100% of patients in our study. However, the levels of the various minerals present in the foods consumed by our patients were not assessed. We thus observed in this study that CKD developed hyperphosphatemia in 48% of the population. Of these 48% with hyperphosphatemia, 56% were on dialysis (stage 5D). Hyperphosphatemia is a frequent complication of chronic renal failure [18,19,20,21]. It is present from the onset of renal disease and affects over 70% of patients by the time it reaches the dialysis stage [22]. Our findings are comparable to those of *Joly LM and colleagues* in France, who reported a 50% prevalence of hyperphosphatemia in patients with impaired renal function [23]. In Côte d'Ivoire, *Mondé AA and colleagues* found a 51.3% prevalence of hyperphosphatemia in patients with chronic renal failure [24]. Phosphate levels depend on the balance between intestinal absorption and renal excretion. The latter also depends on renal filtration, which is modulated by proximal tubular reabsorption, enabling 80% of filtered phosphate to be reabsorbed [25]. When renal function is impaired, excretion will be low, and phosphate levels in the body will rise. Moreover, the diet is a major source of phosphates. Fish was eaten by practically the entire population (97.8%), with over 60% consuming meat. Beverages were consumed by 100% of population. It has been reported that up to 60% of phosphate intake is found in preservatives [25]. However, it is very difficult to estimate the amount of dietary phosphate, given the dietary variability of our populations and the lack of maps of nutrient composition of foods in our regions. In view of the literature, the recommended diet to avoid excessive dietary phosphate intake is avoids industrially prepared products rich in preservatives, phosphate- rich soft drinks and reduce animal proteins [26]. In the more advanced stages (5D), the diet remains insufficient to control phosphatemia due to the significant decrease in renal phosphate excretion, and the introduction of binders becomes necessary [25]. Indeed, hyperphosphatemia is considered a major cardiovascular risk factor in CKD, as phosphate has direct vascular toxicity [1,27,28]. In CKD patients, phosphate binders are frequently prescribed to compensate hyperphosphatemia. However, the patients in the present study were not regularly on phosphate binders and dialysis was used to reduce phosphate accumulation. Nevertheless, almost 50% of patients had hyperphosphatemia.

In addition, plasma FGF-23 concentration is controlled by phosphatemia, digestive phosphate intake and calcitriol or 1,25-dihydroxyvitamin D levels, the active form of vitamin D [29,30]. In humans, an increase in digestive phosphate intake elevate plasma FGF-23 concentration. Restriction in digestive phosphate intake is accompanied by a decrease in FGF23 concentration [29]. Hyperphosphatemia leads to increased FGF-23 secretion by osteoblasts and osteocytes [31,32]. As a result, almost half (45.5%) of the study population had elevated FGF-23 levels. This might suggest that as kidney

Table 3. Biological parameters according to sex, to dialysis and to supplementation with furosemide and calcium

Parameters	Women	Men	P value	Dialyzed	Non-dialyzed	P value	Furosemide	No furosemide	P value	Calcium	No calcium	P value
Phosphoremia (mmol/L)	1.4 (±0.4)	1.3 (±0.5)	0.7018	1.4 (±0.5)	1.3 (±0.4)	0.2098	1.5 (±0.5)	1.3 (±0.4)	0.1529	1,4 (±0,5)	1,3 (±0,4)	0,1518
Calcemia (mmol/L)	2.3 (±0.2)	2.3 ± (0.2)	0.8459	2.2 (±0.2)	2.4 (±0.1)	0.0005	2.4 (±0.1)	2.3 (±0.2)	0.1038	2,3 (±0,2)	2,3 (±0,2)	0,0609
Magnesemia (mmol/L)	0.9 (±0.1)	0.9 (±0.1)	0.5826	0.9 (±0.1)	0.9 (±0.1)	0.2648	0.9 (±0.2)	0.9 (±0.1)	0.6974	0,9 (±0,1)	0,9 (±0,1)	0,9315
Vitamin D (ng/mL)	28.4 (±4.3)	26.9 (±5.4)	0.1647	24.3 (±3.1)	31.2 (±4.1)	0.0000	30.0 (±5.6)	26.7 (±4.5)	0.0039	25,1 (±4,0)	29,5 (±5,0)	0,0000
PTH (pg/mL)	77.1 (±22.9)	85.3 (±28.1)	0.1502	99.4 (±16.4)	61.7 (±20.3)	0.0000	67.7 (±27.7)	87.1 (±23.7)	0.0015	96,0 (±19,3)	70,7 (±25,8)	0,0000
FGF-23 (pg/mL)	53.0 (±20.1)	58.8 (±25.3)	0.2528	66.8 (±23.4)	44.4 (±16.5)	0.0000	50.4 (±21.3)	58.6 (±23.8)	0.1405	66,2 (±23,1)	48,6 (±20,5)	0,0003

failure worsens, FGF-23 concentration increases, both through excess synthesis and kidney failure induced retention of FGF-23. Several authors have reported that FGF-23 could be used as a cardiovascular risk marker in CKD [33]. Indeed, in the study of *Isakova T and colleagues*, FGF-23 levels increased with GFR at 57.8 mL/min/1.73 m^2 and PTH increased with GFR at 46.9 mL/ min/1.73 m^2 [34]. Consequently, FGF-23 would be the first to be increased in order to normalize phosphate levels. Calcitriol levels were not assessed in the present study. Nevertheless, the vitamin D level assessed revealed hypovitaminosis D in 66.3% of patients. It has been reported that reduced renal calcitriol synthesis leads to reduced digestive phosphate absorption, but also to reduce intestinal calcium absorption. There is then hypocalcemic tendency associated with secondary hyperparathyroidism [30,34].

As a result, renal cells will no longer be able to perform their functions, and renal calcium leakage will be observed, leading in the long term to hypocalcemia. In our study, almost 45% of the population was on calcium supplementation. Normal calcium levels were obtained in 92% of the population. Normocalcemia in renal failure is not common [24]. In a study conducted in India by Patel DD and colleagues in untreated stage 3 chronic kidney failure patients, they found 61.29% hypocalcemia [35]. However, this calcium supplementation to patients in our study could normalize blood calcium levels in CKD. What's more, in cases of native vitamin D deficiency, either in the form of vitamin D reserve or active vitamin D, normal blood calcium levels are maintained by stimulation of PTH synthesis, with the onset of secondary hyperparathyroidism [36]. In chronic kidney disease, the decrease in GFR may be followed by phospho-calcium disorders, including hypocalcemia due to defective kidney 1α-hydroxylation of calcidiol to calcitriol. In practice, blood calcium levels remain normal until pre-terminal stage, due to secondary hyperparathyroidism. As a result, in this study, calcium levels were significantly lower in dialysis patients than in non-dialysis patients (p=0.0005). Furthermore, there was a positive correlation between the progression of CKD and serum vitamin D deficiency. This corroborates the work of Ghosh et al in 2020 [37]. They reported that vitamin D deficiency was more pronounced in advanced stages of CKD.

5. CONCLUSION

Serum phosphate levels remained high in our study population. Vitamin D deficiency was found in the majority of our patients, possibly due to the progression of CKD and increased serum FGF-23 levels. Nevertheless, this hypovitaminosis D does not reflect the serum calcium concentration of our study population. Normocalcemia was found in almost all our patients, and this could be justified by calcium supplementation and diet. Despite all the therapeutic strategies employed, some patients still presented with phospho-calcium imbalance and associated complications. Consequently, it would be advisable to readjust the management of these patients in order to minimize the effects of hyperphosphatemia and improve their life quality.

6. LIMITATIONS OF THE STUDY

A limitation was lack of conventional list for mineral composition of foods consumed in our study. In addition, the deficiency of cardiovascular imaging to assess the presence of vascular calcifications is a limitation of this study. Despite these limitations, serum phosphate levels remain high in our CKD patients.

CONSENT AND ETHICAL APPROVAL

This work was carried out in accordance with the recommendations of Helsinki Declaration of Ethics on the use of living beings. Also, authorizations from the Heads of hospital centers were obtained. Informed consent was obtained from participants or relatives of people unable to give it themselves. In addition, all participants were guaranteed respect for the confidentiality of data collected during the survey.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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