Phosphocalcic profile of chronic kidney disease at Libreville

ABSTRACT

Introduction: Askidneyfunctiondeclinestowardsthemoreseverestagesofchronickidneydisease (CKD), the interactions between kidney, intestine and bone become increasingly unstable. CKDwith mineral and bone disorders and secondary hyperparathyroidism would be developing. The aim of this study was to determine thephosphocalcic profile of CKD patients in Libreville.

Material and methods: This was a cross sectional study with 89 CKD patients recruited.A blood sample was taken to measurePTH, vitamin D, FGF-23 by ELISA method; calcium, magnesium, fasting blood glucose, phosphateandcreatinine by spectrophotometer.

Results: Mean phosphorus levels were 1.3 ± 0.5 mmol/L andhormone levels 81.8 ± 26.2 pg/mL and 27.5 ± 5.0ng/mL for PTH and vitamin Drespectively.Significanthyperphosphatemia was found among 43(48.3%;p=0.0135)patients.There were 59 (66.3%)subjectswithhypovitaminosisDp=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-dialysispatients, with a p=0.0000.Vitamin D levels were significantly higher in patients withoutcalcium supplementation (29.5 ± 5.0 ng/mL) than in those with supplementation (25.1 ± 4.0ng/mL,p=0.0000).

Conclusion: Phosphate levels remained high in our study population. Vitamin D deficiency wasfound in the majority of our patients.It would be advisable to readjust themanagement of these patients in order to minimize the effects of hyperphosphatemia andimprovelife 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 toa 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. MATERIELS AND METHODS

2.1 Study site

This was a 3-month cross-sectional study, whichranfrom1st December2022to 28th February2023.Patients were recruited at the *Centre National d'Hemodialyse(CNH)* of *the Centre HospitalierUniversitaire de Libreville (CHUL)*. Biological assays were performed at the BiochemistryLaboratory of the University of Health Sciences and at the National Public Health Laboratoryin Libreville.

2.2Study population

Patients included were chronic kidney disease stage 3-5 on dialysis or not. There was nogender distinction, and age was greater than or equal to 15 years. They were included aftergiving their informed consent afterexplanation the study aim. Pregnantandbreast-feedingwomenwereexcludedfromthestudy.

Socio-clinical data werecollected.A blood sample was taken to measurePTH, vitamin D, FGF-23, blood calcium, blood magnesium, fasting blood glucose, bloodphosphateandserumcreatinine.A24-hoururinesamplewastakenforphosphatedetermination.

2.3Biological assays

2.3.1Determinationofminerals,bloodsugarand renalfunctionparameters

Calcemia,phosphatemia,magnesemia,glycemia,creatinemiaandphosphaturiaweredetermined spectrophotometrically using standard methods[11-14]. Glomerular filtration rate wasdetermined according to CKD-EPI (chronic kidney disease epidemiology collaboration) [15].

2.3.2 Hormones assays

PlasmaassaysforvitaminD,FGF-23andPTHwereperformedbyELISAusingkitsrecommended by themanufacturer.

2.4Statistical 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 tocompareproportions.Relationshipsbetweenqualitativeandquantitativevariableswerestudied using the Pearson test. The difference was statistically significantwhen the P value waslessthan 0.05.

3. RESULT

Themeanageofthepopulationwas54.5±15.8years,withasystolicbloodpressureof148 ± 21.0 mmHg. People aged 40-59 were more affected by chronic kidney failure. However, in theunder-40s,16.9%hadCKD(Table1).Furthermore,thestudypopulationcomprised52(58.4%) men and 37 (41.6%) women p=0.0355. There were more hypertensive (83.1%;p=0.0000)followedbydiabetics.Inthissample,77(86.5%)patientswereonironsupplement ation, 39 (43.8%) were on calcium supplementation and 24 (27.0%) were onfurosemide. 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 theentirepopulationfrequently **(Table1)**.

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)	0.1595
60-74	27 (30.3)	
≥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%)	

In the study population, mean phosphorus levels were 1.3 ± 0.5 mmol/L, with extremesranging from 0.4 to 3.0 mmol/L. Mean hormone levels were 81.8 ± 26.2 pg/mL and 27.5 ± 5.0ng/mL for serum PTH (extremes ranging from 23.4 to 120.2 pg/mL) and serum vitamin D(extremesrangingfrom20.1to39.4ng/mL)respectively.Meanglomerularfiltrationratewas15.7 ± 12.8 mL/min/1.73 m^2 , with extremes ranging from 2.4 to 53.3 mL/min/1.73

m^2**(Table2)**.Intermsoffrequency,43(48.3%;p=0.0135)hadsignificanthyperphosphatemia.Inaddition, 40 (45.5%; p=0.1771) patients had elevated FGF-23 levels. There were 59 (66.3%)subjectswithhypovitaminosisDp=0.0000.PTHlevelswereelevatedin61(68.5%;p=0.0000) subjects. Less than 50% of patients had normal blood glucose levels (p=0.0034)**(Table2).**

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)	
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)	
		45 (50.6)	

Normal

GFR : glomerular filtration rate

Serum phosphorus levels were 1.4 ±0.4 in women and 1.3 ±0.5 in men (p=0.7018). Meanserum calcium was comparable in both sexes (p=0.8459). Serum FGF-23 was 53.0 ± 20.1ng/mlin womenand58.8±25.3 inmen (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-dialysispatients, with a p=0.0000 value. Similarly, serum vitamin D levels were significantly higher innon-dialysis patients (31.2 ± 4.1 ng/mL) than in dialysis patients (24.3 ± 3.1 ng/mL), with ap=0.0000 value.Serum magnesiumlevelswerecomparableindialysisandnon-dialysispatients (p=0.2648). A mean serum calcium level of 2.2 ± 0.2 mmol/L was found in dialysissubjectsand2.4±0.1mmol/Lin non-dialysissubjects,with ap=0.0005value**(Table3)**.

Serum vitamin D levels were significantly higher in subjects taking furosemide 30.0 ± 5.6ng/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/Lcompared withthosetaking furosemide67.7±27.7pg/mL foravalueofp=0.0015**Table3**.

Mean serum calcium levels in calcium-supplemented and non-supplemented patients werecomparable (p= 0.0609). Serum vitamin D levels were significantly higher in patients withoutcalcium supplementation (29.5 ± 5.0 ng/mL) than in those with supplementation (25.1 ± 4.0ng/mL,p=0.0000).Nevertheless,serumPTHlevelswere96.0±19.3pg/mLinthesupplemented subjects and 70.7 ± 25.8 pg/mL in the non-supplemented subjects (p= 0.0000)(**Table3)**.

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

4. DISCUSSION

In this study, the average age of the patients was 54.5 ±15.8 years, with extremes rangingfrom 18 to 89 years, and they were predominantly male. The young age of 18 indicates aserioussituation.Thissuggeststheneedforearlierpreventivemeasurestoraiseawareness of hypertension and diabetes, as these two parameters were the most commoncontributors to the onset of CKD. These results are similar to those of Ramilitiana andcolleagues, in 2016 [16]. This male predominance may be explained by the fact that womenare less likely to develop CKD and reach end-stage renal failure than men, as the decline inrenalfunctionisslowerinwomen[17].

The deterioration in renal function will have an impact on the majority of minerals, due totheir excretion from the body, mainly via the urine. Nevertheless, serum magnesium levelswere normal in the majority of patients (88.8%). This could be explained on the one hand byfractional excretion of magnesium to compensate for reduced dietary intake, and on theother by preserved transcellular intestinal absorption. The magnesium concentration of thedialysatecouldalsobeconsidered.Inaddition,starchyfoodsandmagnesium-richvegetables were consumed by almost 100% of patients in our study. However, the levels ofthe various minerals present in the foods consumed by our patients were not assessed.

WethusobservedinthisstudythatCKDdevelopedhyperphosphatemiain48%ofthepopulation.Ofthese48%withhyperphosphatemia,56%wereondialysis(stage5D).Hyperphosphatemia is a frequent complication of chronic renal failure [18-19, 20-21]. It ispresent from the onset of renal disease and affects over 70% of patients by the time itreaches the dialysisstage [22]. Our findingsare comparable to those of*Joly LM andcolleagues* in France, who reported a 50% prevalence ofhyperphosphatemia in patientswith impaired renal function [23]. In Côte d'Ivoire, *Mondé AA and colleagues* found a 51.3%prevalence ofhyperphosphatemia in patients with chronic renal failure[24]. Phosphatelevels depend on the balance between intestinal absorption and renal excretion. The latteralsodependsonrenalfiltration,whichismodulatedbyproximaltubularreabsorption,enabling 80% of filtered phosphate to be reabsorbed [25]. When renal function is impaired,excretionwillbelow,andphosphatelevelsinthebodywillrise.Moreover,thedietisamajorsourceofphosphates.Fishwaseatenbypractictheentirepopulation(97.8%),with over 60% consuming meat. Beverages were consumed by 100% of population. It hasbeen reported that up to 60% of phosphate intake is found in preservatives [25]. However, itis very difficult to estimate the amount of dietary phosphate, given the dietary variability ofour

populations and the lack of maps of nutrient composition of foods in our regions.Inviewoftheliterature,therecommendeddiettoavoidexcessivedietaryphosphateintake is avoids industrially prepared products rich in preservatives, phosphate-richsoftdrinksandreduce animalproteins[26]. Inthemoreadvancedstages(5D),thedietremainsinsufficienttocontrolphosphatemiaduetothesignificantdecreaseinrenalphosphateexcretion,andtheintroductionofbindersbecomesnecessary[25].Indeed,hyperphosphatemiaisconsidered 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 compensatehyperphosphatemia.However,thepatientsinthepresentstudywerenotregularlyon phosphate binders and dialysis was used to reduce phosphateaccumulation.Nevertheless, almost 50%ofpatientshadhyperphosphatemia.

Inaddition,plasmaFGF-23concentrationiscontrolledbyphosphatemia,digestivephosphateintakeandcalcitriolor1,25-dihydroxyvitaminDlevels,theactiveformofvitaminD [29-30]. In humans, an increase in digestive phosphate intake elevate plasma FGF-23concentration. Restriction in digestive phosphate intake is accompanied by adecrease inFGF23 concentration[29].Hyperphosphatemia leads to increasedFGF-23secretion by osteoblastsandosteocytes[31-32]. As a result,almosthalf(45.5%)ofthestudypopulationhadelevatedFGF-23levels.Thismightsuggestthataskidneyfailure worsens, FGF-23 concentration increases, both through excess synthesis and kidney failure inducedretentionofFGF-23.SeveralauthorshavereportedthatFGF-23couldbeusedas 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 withGFRat46.9mL/min/1.73m^2[34].Consequently,FGF-23wouldbethefirsttobeincreasedinordertonormalizephosphatelevels.Calcitriollevelswerenot assessed in the present study.Nevertheless,thevitaminDlevelassessedrevealedhypovitaminosisDin66.3%ofpatients.Ithasbeenreportedthatreducedrenalcalcitriolsynthesisleadstoreduceddigestive phosphate absorption, but also to reduce intestinal calcium absorption. There isthen hypocalcemic tendencyassociatedwithsecondaryhyperparathyroidism[30,34].

As a result, renal cells will no longer be able to perform their functions, and renal calciumleakage will be observed, leadingin the long term to hypocalcemia.In our study, almost45%ofthepopulationwasoncalciumsupplementation.Normalcalciumlevelswereobtained 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 3chronic kidney failure

patients, they found 61.29% hypocalcemia [35]. However, this calciumsupplementation 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 reserveoractivevitaminD,normalbloodcalciumlevelsaremaintainedbystimulationofPTH synthesis, with the onset of secondary hyperparathyroidism [36]. In chronic kidney disease,thedecreaseinGFRmaybefollowed byphospho-calciumdisorders,includinghypocalcemia due to defective kidney 1α-hydroxylation of calcidiol to calcitriol. In practice,bloodcalciumlevelsremainnormaluntilpre-terminalstage,duetosecondaryhyperparathyroidism. As a result, in this study, calcium levels were significantly lower indialysis patients than in non-dialysis patients (p=0.0005). Furthermore, there was a positivecorrelationbetweentheprogressionofCKDandserumvitaminDdeficiency.Thiscorrobora tes the work of Ghosh et al in 2020 [37]. They reported that vitamin D deficiencywasmorepronouncedin advancedstagesofCKD.

5. CONCLUSION

Serum phosphate levels remained high in our study population. Vitamin D deficiency wasfound in the majority of our patients, possibly due to the progression of CKD and increasedserumFGF-23levels.Nevertheless,thishypovitaminosisDdoesnotreflecttheserumcalcium concentration of our study population. Normocalcemia was found in almost all ourpatients, and this could be justified by calcium supplementation and diet. Despite all thetherapeuticstrategiesemployed,somepatientsstillpresentedwithphospho-calciumimbalance and associated complications. Consequently, it would be advisable to readjust themanagement of these patients in order to minimize the effects of hyperphosphatemia andimprovetheirlife quality.

6. LIMITATIONS OF THE STUDY

A limitation waslack of conventional list for mineral composition of foodsconsumed in our study.In addition, the deficiency of cardiovascular imaging to assess thepresence of vascular calcificationsisa limitationof thisstudy.Despitethese limitations,serum phosphate levels remain high in our CKD patients.

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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