

# 25 [OH] Vitamin D and Intact Parathyroid Hormone in Congolese Hemodialysis Patients: Evaluation of KDIGO Targets

Samuel Mbadu Lelo<sup>1,2</sup>, François-Pantaléon Musungayi Kajingulu<sup>1,3,4</sup>, Jean-Robert Makulo<sup>1,2</sup>, Yannick Mayamba Nlandu<sup>1,5</sup>, Justine Busanga Bukabau<sup>1,5</sup>, Pierre Koso Mbulupasu<sup>1,6</sup>, Augustin Luzayadio Longo<sup>1</sup>, Jeanine Nina Losa Luse<sup>7</sup>, Vieux Momeme Mokoli<sup>1,2</sup>, Ernest Kiswaya Sumaili<sup>1</sup>, Nazaire Mangani Nseka<sup>1</sup>

<sup>1</sup>Hemodialysis Center, Division of Nephrology, Kinshasa University Hospital, Kinshasa, Democratic Republic of the Congo; <sup>2</sup>Hemodialysis Center, Ngaliema Medical Center, Kinshasa, Democratic Republic of the Congo; <sup>3</sup>Dialysis Center, HJ Hospital, Kinshasa, Democratic Republic of the Congo; <sup>4</sup>Department of Internal Medicine, Saint-Joseph Hospital, Kinshasa, Democratic Republic of the Congo; <sup>5</sup>Hemodialysis Center, Centre Médical de Kinshasa, Kinshasa, Democratic Republic of the Congo; <sup>6</sup>Department of Internal Medicine, Clinique Ngaliema, Kinshasa, Democratic Republic of the Congo; <sup>7</sup>Hemodialysis Center, Hôpital Général de Référence de Kinshasa, Kinshasa, Democratic Republic of the Congo

Correspondence: Jean-Robert Makulo, Email [jrmakulo2016@gmail.com](mailto:jrmakulo2016@gmail.com)

**Background:** Data on 25 [OH] vitamin D and intact parathyroid hormone [iPTH] in hemodialysis patients are very limited in sub-Saharan African countries. The present study aimed to assess the magnitude of hypovitaminosis D, and to evaluate the achievement of iPTH KDIGO 2017 targets among chronic hemodialysis patients followed in Kinshasa.

**Methods:** We conducted a multicenter cross-sectional study in 6 hospitals in Kinshasa. All patients followed on hemodialysis for more than 3 months were included. Hypovitaminosis D was defined as <30 ng/mL (insufficiency = 20–29 ng/mL; deficiency if <20 ng/mL) and the targets for iPTH values were based on the 2017 KDIGO guidelines. The determinants for hypovitaminosis D were evaluated by logistic regression.

**Results:** 251 patients [mean age 56 ± 14 years, 72.5% men, 63% hypertensive, 31% diabetic, 100% supplemented with native 25 [OH] vitamin D + CaCO<sub>3</sub>] were included. Hypovitaminosis D was found in 79.7% (deficiency 47.4%) and was associated with the male gender aOR 2.7 [1.4–5.2], p = 0.004, the low-permeability dialyzer 2.2 [1.1–4.2], p = 0.025 and anemia 3.9 [1.2–12.7], p = 0.022. Only 40% of patients with 25 [OH] vitamin D deficiency had iPTH according to KDIGO targets vs 6% of patients with severe hyperparathyroidism (iPTH > 600 pg/mL), 45% with levels between 16 and 150 pg/mL and 9% a iPTH ≤ 15 pg/mL.

**Conclusion:** Despite a sunny environment, a large proportion of Congolese hemodialysis patients have hypovitaminosis D, in particular a deficiency. Among them, less than half have target iPTH values. These results show the benefit of regular monitoring of these parameters in order to optimize treatment.

**Keywords:** KDIGO targets, hemodialysis, hypovitaminosis D, iPTH

## Introduction

Several studies show that hypovitaminosis D is common in black populations, both those living in cold and warm regions.<sup>1,2</sup> This difference can be explained by the fact that ultraviolet rays, which are essential for vitamin D synthesis, penetrate black skin less [7.4% UVB] than white skin [24%].<sup>3,4</sup> People with black skin may therefore be deficient in vitamin D if they receive minimal sunlight.<sup>4,5</sup>

The role of the kidney in the synthesis of the active form of vitamin D, 1.25 [OH] D<sub>3</sub>, is crucial. Loss of renal 1- $\alpha$ -hydroxylase activity promotes secondary hyperparathyroidism and mineral-bone disorders [MBD].<sup>6</sup> Fibroblast growth factor 23 [FGF-23], hormone synthesized by osteocytes, has two main actions in the renal proximal tubular cell: inhibition of 1- $\alpha$ -hydroxylase and of apical membrane, the expression of Npt2a/Npt2c co-transporters. This leads to a decrease in 1.25 [OH] D and a phosphaturic effect.<sup>7,8</sup> FGF-23 also acts at the level of the parathyroid by inhibiting

the synthesis of parathyroid hormone [PTH]. Another transmembrane protein that exists in soluble form and is mainly synthesized at the distal tubular level, Klotho, has been shown to be an essential co-factor of FGF-23 activity.<sup>8</sup> Recent studies in mice implicate Wnt inhibitors (portmanteau of wingless and int) in the pathogenesis of CKD-MBD. These Wnt inhibitors, including Dickkopf-1 (Dkk1) and sclerotin, are secreted in kidney disease. Using a monoclonal antibody to reduce their levels improves bone abnormalities.<sup>9</sup> Apart from disorders of the metabolism of calcium, phosphorus, iPTH or vitamin D, abnormalities of bone renewal, mineralization and volume and extraskeletal calcifications (vascular and soft tissues) are among the complications grouped together under the term CKD-MBD. These abnormalities are associated with increased mortality and morbidity, including fracture risk.<sup>6-9</sup>

Hypovitaminosis D is very common in chronic kidney disease [CKD], especially in hemodialysis patients. Apart from the more pronounced deterioration of renal function recognized at this stage of the disease, other factors contribute to its occurrence. These include the age of patients, which is often higher than the average for the general population, the exposure to the sun due to their reduced mobility, nutritional deficiencies, insufficient vitamin D supplementation.<sup>10,11</sup>

A few rare studies conducted in sub-Saharan Africa [SSA] have reported a frequency of hypovitaminosis D varying between 60 and 80% among chronic hemodialysis patients, often associated with normal or elevated PTH levels.<sup>12-15</sup> The factors associated with this decrease and the concordance between 25 [OH] D levels and expected iPTH values have not yet been studied in our setting.

In order to contribute to the improvement of the management of abnormalities of phosphocalcium metabolism in patients undergoing chronic hemodialysis [HD] in Kinshasa, the objectives of this study were to determine the frequency and determinants of hypovitaminosis D in this population, and to establish the concordance between the results of 25 [OH] D and iPTH levels.

## Methods

### Study Design, Setting and Population

We conducted a cross-sectional study from August 2018 to December 2019 in 6 HD centers in Kinshasa: the HD center of the University of Kinshasa Hospital [UKH], the HD center of Ngaliema Medical Center [NMC], Afia Medical Center [AMC], HJ Hospital, the dialysis center of Kinshasa at the provincial general hospital of Kinshasa [CDK], the HD center of the Congolese National Police Hospital [CNP]. In all these hospitals, 25 [OH] D and PTH were rarely measured and patients followed in chronic HD were systematically supplemented with native vitamin D and CaCO<sub>3</sub> at doses of 400 IU and 500 mg twice daily, respectively. The sample consisted of patients undergoing chronic HD [HD ≥ 3 months] aged over 18 years.

A minimal sample size of 245 participants was calculated according to the formula  $n = Z^2PQ/d^2$  assuming a confidence coefficient (z) of 1.96 for a confidence interval (CI) of 95%, a degree of precision (d) of 5%, Q=1-P and an expected proportion (p) of patients presenting abnormalities in phospho-calcium metabolism is 0.8, referring to the result found by Bala W et al in South Africa.<sup>13</sup> The active queue of patients followed for hemodialysis in these 6 hospitals being 251, we opted for exhaustive sampling.

### Data Section

Sociodemographic data [age, sex, educational level] and medical history were collected, including the search for pathological fractures documented in the medical file. Apart from 25[OH] D, the other parameters of interest were: ionized calcium, phosphorus, intact parathyroid hormone [iPTH], blood count, lipid profile and HD treatment modalities. The specific parameters during the HD sessions were: the patient's estimated dry weight, height and body mass index [BMI], the number of HD sessions per week, the calcium concentration of the dialysis bath prescribed to the patient [Ca<sup>++</sup>1 mmol/L, Ca<sup>++</sup>1.25 mmol/L, Ca<sup>++</sup>1.5 mmol/L or Ca<sup>++</sup>1.75 mmol/L], the type of dialysis bath acid prescribed to the patient [bicarbonate with acetic acid, bicarbonate with hydrochloric acid, bicarbonate with citric acid, bicarbonate without acid, acetate], the type of machine used during the dialysis session [conventional hemodialysis machine = HD, hemodiafiltration machine = HDF], the type of dialyzer used during the HD session [low permeability dialysis, high permeability dialysis].

The patient's blood samples were collected fasting before the HD session in dry tubes (just before the first dialysis session of the week). They were kept cold and sent the same day to the HJ Hospital laboratory for analysis. Ionized blood

calcium was determined by the direct potentiometric method using a Cobas 6000 device. The determination of phosphatemia was carried out by the spectrophotometric method using a Cobas c 311<sup>®</sup>. The determination of 25 [OH] D and iPTH was performed by the chemiluminescence method using a Cobas c 411<sup>®</sup> device. The lipid profile and the hemogram were carried out using the usual methods.

## Definitions

Hypovitaminosis D was defined as insufficiency if 25 [OH] D level between 20–29 ng/mL and deficiency if < 20 ng/mL.<sup>16</sup> Ionized hypercalcemia: calcium > 1,3 mmol/L.<sup>16</sup> Ionized hypocalcemia: calcium < 1.05 mmol/L.<sup>16</sup> Hyperphosphatemia: > 1.5 mmol/L.<sup>16</sup> Hypophosphatemia: < 0,8 mmol/L.<sup>16</sup> iPTH values exposing the HD patient to low bone remodelling: < 150 pg /mL.<sup>17</sup> iPTH values exposing to rapid bone remodelling: > 600 pg /mL.<sup>17</sup> Recommended iPTH values in HD patients: iPTH between 151–600 pg /mL (values ranging from 2 to 9 times the upper normal limit).<sup>17</sup> Low iPTH: ≤ 15 pg /mL.<sup>18</sup> High phospho-calcium product [PxCa]: value ≥ 4.51 mmol<sup>2</sup> /L.<sup>19</sup> Anemia: Hb < 13 g/dL in men and < 12 g/dL in women.<sup>20</sup> Total hypercholesterolemia: ≥ 150 mg/dL,<sup>21</sup> Hypertriglyceridemia: ≥ 150 mg/dL,<sup>21</sup> high LDL-c: ≥ 100 mg/dL,<sup>21</sup> low HDL-c: < 40 mg/dL in men and < 50 mg/dL in women.<sup>21</sup>

## Statistical Analyses

Validated data were compiled into Excel and analyzed using SPSS software version Windows 21.0. The qualitative variables are described in terms of proportions or percentages and the quantitative variables in terms of means ± standard deviation. The Pearson chi-square test or Fisher's exact test [for small numbers] was used to compare proportions. The Student *t* test was used to compare the means of the variables when the distributions were Gaussian. The Pearson's correlation coefficient was calculated to assess the relationship between two continuous variables. The relative contribution of each risk factor for hypovitaminosis D was studied by multivariate logistic regression, using the stepwise descending method. The coefficients obtained by the logistic regression were used to calculate the Odds ratio [OR] and the 95% confidence interval [CI]. For the selection of variables in the logistic regression model, the minimum threshold of significance to enter the model was 0.05 and a variable whose significance level reached 0.10 had to be removed from the model. The value  $p < 0.05$  defined the statistical significance level.

## Ethical Considerations

The ethical principles applicable to medical research involving human beings have been in accordance with the Declaration of Helsinki developed by the World Medical Association. Patients were recruited on the basis of free and informed consent, and the confidentiality of all personal information of the patients was respected. The study protocol was submitted to the ethics committee of the Kinshasa School of Public Health for review and Kinshasa for analysis and received approval registered at number ESP/CE/053/2016.

## Results

The present study included 251 patients, 182 of whom were male [72.5%]. The patients were relatively young [mean age = 56±14 years]; 63% were hypertensive 31% were diabetic. Apart from the level of education, financing of care, alcohol and tobacco, no difference was observed between men and women [Table 1].

Concerning data on HD technique, 71% of the patients were under HD and 29% alternated conventional HD and HDF. The Ca<sup>++</sup> 1.75 bath was used in 29% of patients vs 71% with a 1.5 Ca<sup>++</sup> bath. More than two thirds of patients [71%] used a low-permeability filter while 29% of patients used a high-permeability filter. Anemia was present in 94% of patients and HDL hypocholesterolemia [75%] was the most common lipid disorder. HIV [2%], HCV [4%] and HBV [2%] infections were uncommon. Mean ionized calcium, phosphorus, and iPTH were not elevated, with no statistically significant difference between men and women [ $p < 0.05$ ]. The mean 25 [OH] vitamin D level was 22.6±15.1 ng/mL, with lower values in men, 21.1±14.5 ng/mL vs 26.6±16.5 ng/mL in women [ $p=0.017$ ] [Table 2].

The 25 [OH] vitamin D was negatively correlated with iPTH [ $r = -0.166$ ,  $p = 0.008$ ] and phosphatemia [ $r = -0.267$ ,  $p < 0.001$ ] vs a positive correlation with PxCa [ $r = 0.252$ ,  $p < 0.001$ ]. Hypovitaminosis D was found in 79.7% of patients, with 32.3% having insufficiency and 47.4% having deficiency.

**Table 1** Sociodemographic Characteristics of Patients

Variables	Whole Group n=251	Men n=182	Women n=69	p
Age years old	56 ± 14	57 ± 14	53 ± 14	0.053
Age < 40	37 [15]	24 [13]	13 [19]	0.435
40–59	103 [41]	74 [41]	29 [42]	
≥ 60	111 [44]	84 [46]	27 [39]	
Financing of care	80 [32]	66 [36]	14 [20]	0.010
Higher and universities studies	133 [53]	113 [62]	20 [29]	< 0.001
Hypertension	157 [63]	115 [63]	42 [61]	0.422
Diabetes mellitus	78 [31]	56 [31]	22 [32]	0.489
Tobacco	51 [20]	49 [27]	2 [3]	< 0.001
Alcohol	118 [47]	102 [56]	16 [23]	< 0.001
Obstructive uropathy	5 [2]	3 [2]	2 [3]	0.420
BMI Thinness	25 [10]	13 [7]	12 [17]	0.094
Normal weight	144 [57]	109 [60]	35 [51]	
Overweight	60 [24]	45 [25]	15 [21]	
Obesity	22 [9]	15 [8]	7 [10]	

**Notes:** Results expressed either as mean ± standard deviation or as absolute frequency (percentage).

**Abbreviation:** BMI: body mass index.

**Table 2** Biological Characteristics and Dialysis Parameters of Patients

Variables	Whole Group n=251	Men n=182	Women n=69	p
Hb, g/dl	8.5 ± 1.9	8.6 ± 2.0	8.4 ± 1.7	0.522
Anemia	237 [94]	173 [95]	64 [93]	0.332
Hct, %	25.8 ± 6.2	26.2 ± 6.3	24.7 ± 6.0	0.144
WBC/mm <sup>3</sup>	7753 ± 4353	7800 ± 4513	7637 ± 3972	0.824
WBC < 4000/mm <sup>3</sup>	24 [10]	16 [9]	8 [12]	0.694
WBC 4000–10,000/mm <sup>3</sup>	174 [69]	125 [69]	49 [71]	
WBC > 10,000 /mm <sup>3</sup>	53 [21]	41 [23]	12 [17]	
Platelets < 1.5 × 10 <sup>3</sup> /mm <sup>3</sup>	229 ± 87	220 ± 84	247 ± 90	0.162
Total cholesterol ≥ 150 mg/dL	38 [15]	29 [16]	9 [13]	0.362
LDLc ≥ 100 mg/dL	83 [33]	68 [37]	15 [22]	0.013
HDLc < 40 mg/dL [man], < 50 mg/dL [woman]	187 [75]	140 [77]	47 [68]	0.104
TG ≥ 150 mg/dL	73 [29]	47 [26]	26 [38]	0.047
HIV antibodies	6 [2]	4 [2]	2 [3]	0.529
HCV antibodies	11 [4]	8 [4]	3 [4]	0.641
HbS antigen	6 [2]	4 [2]	2 [3]	0.529
Ionized calcium	0.98 ± 0.38	0.97 ± 0.31	0.99 ± 0.52	0.801
Phosphatemia	2.57 ± 1.79	2.58 ± 1.85	2.56 ± 1.63	0.950
25 [OH] D	22.6 ± 15.1	21.1 ± 14.5	26.6 ± 16.5	0.017
iPTH	192 ± 251	203 ± 252	163 ± 249	0.258
HD	178 [71]	131 [72]	47 [68]	0.325
HD + HDF	73 [29]	51 [28]	22 [32]	
Bath Mg <sup>++</sup> 0.5	73 [29]	51 [28]	22 [32]	0.325
Bath, Mg <sup>++</sup> 1	178 [71]	131 [72]	47 [68]	
Bath, Ca <sup>++</sup> 1.75	73 [29]	51 [28]	22 [32]	0.325
Bath, Ca <sup>++</sup> 1,5	178 [71]	131 [72]	47 [68]	
Bath, Cl <sup>-</sup> 107	73 [29]	51 [28]	22 [32]	0.325

(Continued)

**Table 2** (Continued).

Variables	Whole Group n=251	Men n=182	Women n=69	p
Bath, Cl <sup>-</sup> 91	178 [71]	131 [72]	47 [68]	0.325
Bath, Na <sup>+</sup> 138	73 [29]	51 [28]	22 [32]	
Bath, Na <sup>+</sup> 140	178 [71]	131 [72]	47 [68]	
Bath, bicarbonate 32	73 [29]	51 [28]	22 [32]	0.325
Bath, Bicarbonate 35	178 [71]	131 [72]	47 [68]	
High permeability dialyzer	76 [29]	53 [29]	23 [33]	0.308
Low permeability dialyzer	175 [71]	129 [71]	46 [67]	
≤ 1 session per week	63 [25]	42 [23]	20 [29]	0.589
2 sessions per week	23 [9]	18 [10]	5 [7]	
≥ 3 sessions per week	165 [66]	122 [67]	44 [64]	

**Notes:** Results expressed either as mean ± standard deviation or as absolute frequency [percentage].

**Abbreviations:** Hb, hemoglobin; HbS, hepatitis B surface; Hct, hematocrit; HD, hemodialysis; HDF, hemodiafiltration; WBC, white blood cells; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; HIV, human immunodeficiency virus; HCV, hepatitis C virus; iPTH, intact parathyroid hormone; 25 [OH] D, 25 hydroxy vitamin D.

Table 3 shows that 11 patients [9%] with 25[OH]D deficiency had low iPTH level vs 53 patients [45%] a iPTH between 16 and 150 pg/mL vs 48 patients [40%] a iPTH 151–600 pg/mL, and only 7 patients [6%] had iPTH > 600 pg/mL. Among patients with 25(OH)D insufficiency, 4 [5%] had low PTHi level vs 13 patients [16%] a iPTH between 16 and 150 pg/mL and 62 patients [77%] a iPTH between 151–600 pg/mL, and only 2 patients [2%] had a iPTH > 600 pg/mL. Among patients with normal 25 [OH] D levels, 6 patients [12%] had low iPTH levels, 2 patients [4%] had iPTH > 600 pg/mL and 30 patients [59%] had iPTH levels between 16 and 150 pg/mL.

In the multivariate logistic regression model, male sex [aOR 2.7 [1.4–5.2], p = 0.004], low-permeability dialyzer [aOR 2.2 [1.1–4.2], p = 0.025] and anemia [aOR 3.9 [1.2–12.7], p = 0.022] were associated with hypovitaminosis D [insufficiency and deficiency]. Table 4 shows that hyperphosphatemia was near to statistical significance [aOR 2.0; 95% CI [1.0–5.0], p = 0.053].

**Table 3** Number of Patients Achieving 2017 KDIGO Targets and Vitamin D Status

	iPTH			
	≤ 15 pg/mL	16–150 pg/mL	151–600 pg/mL	> 600 pg/mL
25 [OH] D, deficiency	11	53	48	7
Insufficiency	4	13	62	2
Normal value	6	30	13	2
Total	21	96	123	11

**Abbreviation:** 25 [OH] D, 25 hydroxy vitamin D.

**Table 4** Factors Associated with Hypovitaminosis D in Chronic Hemodialysis Patients

	Univariate Analysis			Multivariate Analysis		
	OR	CI 95%	p	aOR	CI 95%	P
Hyperphosphatemia vs no	2.0	1.0–3.3	0.043	2.0	1.0–5.0	0.053
Male vs female sex	2.8	1.4–5.2	0.002	2.7	1.4–5.2	0.004
Low permeability dialyzer vs high permeability	2.3	1.2–4.3	0.010	2.2	1.1–4.2	0.025
Anemia vs no	4.4	1.5–13.1	0.005	3.9	1.2–12.7	0.022
Obesity vs no	2.5	1.0–6.2	0.050	–	–	–
Bath, Ca <sup>++</sup> 1.5 vs 1.75	2.2	1.2–4.2	0.013	–	–	–
Bath, bicarbonate 32 vs 35	0.5	0.2–0.9	0.013	–	–	–
HD vs HD + HDF	2.2	1.2–4.2	0.013	–	–	–

Only one case of pathologic fracture was documented by CT scan in a 56 years old woman with hypocalcemia ionized 0.59 mmol/L, phosphatemia 3.6 mmol/L, hypovitaminosis D 21 ng/L, and iPTH 522 pg/mL.

## Discussion

The present multicenter study conducted in the HD centers of Kinshasa revealed that 4 out of 5 patients present a hypovitaminosis D and confirmed some determinants already reported in the literature. Other determinants found in present study, such as male and anemia gender, are unusual. Only half of the patients had iPTH values recommended by the 2017 KDIGO guidelines. Notwithstanding suboptimal patient management, only one case of pathologic fracture was reported.

The similarly high incidence of hypovitaminosis D that we describe is within the range of the results reported in the few studies conducted in SSA in hemodialysis patients.<sup>12–15</sup> Apart from the risk of bone fragility, this complication exposes patients to decreased muscle tone, the occurrence of tetany and seizures [in relation to hypocalcemia], hypocalcemia, an increased risk of cancer, diabetes, depression and autoimmune diseases.<sup>22</sup>

Considering the significant extrarenal production of 1, 25 [OH] D even in advanced CKD, the KDIGO experts recommend supplementing dialysis patients with 25 [OH] D.<sup>17</sup> Since the HD centers in Kinshasa comply with these recommendations, a lower frequency of 25 [OH] D deficiency would be expected, which was not the case. It could be that patients are not compliant with compliant or that the doses used were simply low in a setting where health care is not context reimbursed in the DR Congo and native vitamin D supplementation in these HD centers is rarely supported by regular paraclinical examinations. It is advisable to perform an overall serum 25 [OH] D measurement in all dialysis patients prior to initiation of therapy. A second determination is recommended after three to four months and then once a year to adjust doses and to check compliance.<sup>17</sup> The local marketing of highly concentrated oral ampoules or highly concentrated drops of native vitamin D, which can be administered once or twice a month could help to improve compliance and thus reduce the frequency of hypovitaminosis in dialysis patients in our setting.<sup>23</sup>

For patients with normal 25 [OH] D levels, excessive supplementation exposes them to overdose of vitamin D, which may be manifested by loss of appetite, nausea, vomiting, weakness and nervousness.<sup>24</sup> In the present study, this group represented 21%. Of these, 12% had an iPTH  $\leq$  15 pg/mL [= hypoparathyroidism] and 59% had a value between 16 and 150 pg/mL [Table 3]. Given the risk of adynamic osteopathy, it is logical to stop supplementation [native vitamin D or 1-alpha derivatives] and schedule a next control of 25 [OH] D. Calcium salts and dialysate calcium content should also be reconsidered. The association between hyperphosphatemia and hypovitaminosis D is classic in CKD.

Indeed, in the early stages of CKD, in response to hyperphosphatemia resulting from glomerular filtration, FGF23 and Klotho are secreted and exert a phosphaturic effect.<sup>7,8</sup> On the other hand, FGF23 inhibits 1- $\alpha$ -hydroxylase and the secretion of iPTH. Klotho, FGF23, iPTH and 1- $\alpha$ -hydroxylase thus interact in a complex manner to maintain normal blood calcium levels and to limit the rise in plasma phosphate.

It is known that hypovitaminosis D is very frequent in the elderly, particularly in postmenopausal women. Many recent studies report deficiencies that are surprisingly endemic even in apparently healthy populations, including men.<sup>25</sup> In the studies conducted in hemodialysis patients, we did not find those that report a greater risk of hypovitaminosis D in men. Given the small sample size [only 182 men and 69 women], it would be appropriate to conduct a study with a conduct a study with a larger sample size to verify our results.

HD membranes [dialyzers] are classified as high or low permeability based on their ability to remove uremic toxins and other molecules according to their molecular weight. Inflammatory cytokines and uremic toxins inhibit 25-hydroxylase, which is essential for the synthesis of 25-OH vitamin D.<sup>26</sup> It has been suggested that the removal of medium molecules through high permeability dialyzers may better reflect normal renal function and function and improve clinical outcomes in dialysis patients. Several of these mechanisms could explain the association found between hypovitaminosis D and the use of the use of low-permeability dialyzers.

Both anemia and hypovitaminosis D are frequently described in the general population and in HD patients. While it is true that in CKD, their co-existence is primarily explained by the alteration of renal functions, many authors also underline the reciprocal interactions between the two complications. Hypovitaminosis D, due to of bone remodelling, can

disrupt erythropoiesis.<sup>27</sup> On the other hand, a recent animal model study has shown that correction of anemia by the administration of erythropoietin lowers FGF23 which plays a role in the metabolism of vitamin D.<sup>28</sup>

The negative correlation found between 25 [OH] D and iPTH accounts for the pathophysiology of CKD. With such high frequencies of hypocalcemia, hyperphosphatemia and hypovitaminosis D, one would expect a greater number of patients with severe iPTH. However, at the threshold defined by the 2017 KDIGO group [iPTH > 9 times the normal value],<sup>17</sup> only 4.4% of patients had iPTH > 600 pg/mL. In contrast to our results, a study conducted in Ivory Coast reported 30% of cases of iPTH > 600 pg/mL in HD patients.<sup>15</sup> It cannot be excluded that drug factors may influence the level of iPTH/mL in our patients. Indeed, it is known that calcium-rich dialysis baths, high permeability dialyzers, calcimimetics or vitamin D analogues contribute to decrease the iPTH level.<sup>29</sup> Notwithstanding this hypothesis, it should be recognized that there is no consensus on the ideal level of iPTH. The 2017 KDIGO Working Group considered that modest increases in iPTH may simply represent an adaptive response to declining renal function due to phosphaturic effects and increased bone resistance to PTHi. The only case of pathologic fracture was reported in a patient with hypovitaminosis D, hypocalcemia, hyperphosphatemia, and an iPTH level of 522 pg/mL.

The profile of the patients in this study [relatively young and predominantly male, two-thirds hypertensive and one-third diabetic, almost all anemic, almost two-thirds without funding, many of them not having three HD sessions per week and some treated with low-permeability dialysis machines] corroborates data from previous studies in DRC and some SSA countries.<sup>30</sup>

The results of this study must be interpreted with some limitations. The markers of phosphocalcic metabolism were measured only once, and it is recommended to perform several examinations [especially for iPTH] before concluding.<sup>17</sup> For a complete focus, measurement of bone alkaline phosphatase, FGF-23, Klotho, and other markers of bone turnover would allow for better interpretation of results. The same is true for the evaluation of vascular calcifications and bone biopsy, which were not part of the subject of this study. The main strength of the study is that it is one of the few to address the subject in a multicenter setting in SSA. The laboratory methods used [chemiluminescence] to determine 25 [OH] D and iPTH are among the most recent and currently recommended. The study was able to demonstrate the extent of the disorders of phosphocalcic metabolism and their Risk factors in hemodialysis patients followed in DR Congo.

## Conclusion

Despite a sunny environment, a large proportion of Congolese hemodialysis patients have hypovitaminosis D, in particular a deficiency. Among them, less than half have target iPTH values. These results show the benefit of regular monitoring of these parameters in order to optimize treatment.

## Data Sharing Statement

The database is available from the corresponding author on reasonable request.

## Ethical Rules

The ethical principles applicable to medical research involving human beings were respected in accordance with the Declaration of Helsinki. Patients were recruited on the basis of free and informed consent, and the confidentiality of all personal information was respected. The protocol was submitted to the ethics committee of the Kinshasa School of Public Health for review and had received approval registered at number ESP/CE/053/2016.

## Acknowledgments

The authors thank the heads of all hospitals for permission to collect the data. Yannick Mopango Engole, Evariste Mukendi Kadima, Matthieu Muna Ngilibuma and Serge Mukengabantu Kabangu had helped select the patients.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

The study did not receive funding from any donor, laboratory or pharmaceutical company.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Gutierrez OM, Farwell WR, Kermah D, Taylor EN. Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. *Osteoporos Int*. 2011;22(6):1745–1753. doi:10.1007/s00198-010-1383-2
- Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. *J Bone Miner Res*. 2011;26(6):1368–1376. doi:10.1002/jbmr.309
- Brenner M, Hearing V. The Protective Role of Melanin against UV Damage in Human Skin. *Photochemistry and Photobiology*. 2008;84(3):539–549. doi:10.1111/j.1751-1097.2007.00226.x
- Prentice A, Schoenmakers I, Jones KS. Vitamin D deficiency and its health consequences in Africa. *Clin Rev Bone Mineral Metabol*. 2009;7:94–106. doi:10.1007/s12018-009-9038-6
- Gupta A, Kallenbach LR, Zasuwa G, Divine GW. Race is a major determinant of secondary hyperparathyroidism in uremic patients. *J Am Soc Nephrol*. 2000;11(2):330–334. doi:10.1681/ASN.V112330
- Jean G, Chazot C. Complications and therapeutic management of abnormalities phospho-calcium metabolism in chronic renal failure. *Néphrol Ther*. 2019;15(4):2424–24258.
- Mace ML, Olgaard K, Lewin E. New aspects of the kidney in the regulation of FGF-23 and mineral homeostasis. *Int J Mol Sci*. 2020;21(22):8810. doi:10.3390/ijms21228810
- Hu MC, Kuro-o M, Moe O. Klotho and chronic kidney disease. *Contrib Nephrol*. 2013;180:47–63.
- Fang Y, Ginsberg C, Seifert M, et al. CKD-induced wingless/integration1 inhibitors and phosphorus cause the CKD-mineral and bone disorder. *J Am Soc Nephrol*. 2014;25(8):1760–1773. doi:10.1681/ASN.2013080818
- LaClair RE, Hellman RN, Karp SL, et al. Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. *Am J Kidney Dis*. 2005;45(6):1026–1033. doi:10.1053/j.ajkd.2005.02.029
- Holick M, Chen T. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008;87(4):1080S–1086S. doi:10.1093/ajcn/87.4.1080S
- Toukara AA, Coulibaly AM, Coulibaly N, Traoré B, Maiga MK. Management of chronic hemodialysis patients with anemia: case study conducted in the Department of Nephrology and Hemodialysis at the University Hospital Point G in Mali. *PAMJ*. 2017;26:167. doi:10.11604/pamj.2017.26.167.10861
- Bala W, Raquel D, Saraladevi N. Biochemical markers of mineral bone disorder in South African patients on maintenance haemodialysis. *Afri Health Sci*. 2017;17(2):445–452. doi:10.4314/ahs.v17i2.19
- Seck SM, Dahaba M, Ka EF, Cisse MM, Gueye S, Tal AOL. Mineral and Bone Disease in Black African Hemodialysis Patients: a report from Senegal. *Nephro-Urology*. 2012;4(4):613–616.
- Cavalier E, Yayo ES, Attoungbre-Hauhouot ML, et al. Vitamin D, bone alkaline phosphatase and parathyroid hormone in healthy subjects and haemodialysed patients from West Africa: impact of reference ranges and parathyroid hormone generation assays on the KDIGO guidelines. *Clin Kid J*. 2019;12: 2:288–293. doi:10.1093/ckj/sfy074
- Adams J, Hewison M. Update in Vitamin D. *J Clin Endocrinol Metab*. 2010;95:471–478. doi:10.1210/jc.2009-1773
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7:1–59. doi:10.1016/j.kisu.2017.04.001
- Lee SA, Lee MJ, Ryu GW, et al. Low serum intact parathyroid hormone level is an independent risk factor for overall mortality and major adverse cardiac and cerebrovascular events in incident dialysis patients. *Osteoporos Int*. 2016;27(9):2717–2726. doi:10.1007/s00198-016-3636-1
- Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31:607–617. doi:10.1053/ajkd.1998.v31.pm9531176
- Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Supplements*. 2012;2(4):279–335.
- Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
- Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15(8):2208–2218. doi:10.1097/01.ASN.0000133041.27682.A2
- Jean G, Souberbielle JC, Chazot C. Monthly cholecalciferol administration in haemodialysis patients: a simple and efficient strategy for vitamin D supplementation. *Nephrol Dial Transpl*. 2009;24:3799–3805. doi:10.1093/ndt/gfp370
- Gupta AK, Jamwal V, P M. Hypervitaminosis D and systemic manifestations: a comprehensive review. *JIMS*. 2014;27:236–237.
- Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free living healthy young adults. *Am J Med*. 2002;112(8):659–662. doi:10.1016/S0002-9343(02)01091-4
- Ernandez T, Stoermann-Chopard C. Vitamin D and chronic renal failure: renewed interest in a forgotten vitamin. *Swiss Med J*. 2012;361.



27. Icardi A, Paoletti E, De Nicola L, Mazzaferro S, Russo R, Cozzolino M. Renal anaemia and EPO hyporesponsiveness associated deficiency: the potential role of inflammation. *Nephrol Dial Transplant*. 2013;28(7):1672–1679. doi:10.1093/ndt/gft021
28. Noonan ML, Clinkenbeard EL, Ni P, et al. Erythropoietin and a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHDi) lowers FGF23 in a model of chronic kidney disease (CKD). *Physiological Reports*. 2020;8:e14434. doi:10.14814/phy2.14434
29. Zhan Z, Smyth B, Toussaint ND, Gray NA, Zuo L, de Zoysa JR. Effect of extended hours dialysis on markers of chronic kidney disease-mineral and bone disorder in the ACTIVE Dialysis study. *BMC Nephrol*. 2019;20(1):258. doi:10.1186/s12882-019-1438-3
30. Izeidi PPM, Nlandu YM, Lepira FB, et al. Cost estimate of chronic haemodialysis in Kinshasa, the Democratic Republic of the Congo: a prospective bicentric study. *Hemodial Int*. 2020;24(1):121–128. doi:10.1111/hdi.12802

International Journal of Nephrology and Renovascular Disease

Dovepress

### Publish your work in this journal

The International Journal of Nephrology and Renovascular Disease is an international, peer-reviewed open-access journal focusing on the pathophysiology of the kidney and vascular supply. Epidemiology, screening, diagnosis, and treatment interventions are covered as well as basic science, biochemical and immunological studies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-nephrology-and-renovascular-disease-journal>