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Vitamin D and Parathyroid Hormone Profiles in Living Kidney Failure Patients in Côte d'Ivoire

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Abstract

Introduction: Abnormalities in mineral and bone metabolism, particularly phosphocalcic metabolism, are common in renal failure and are associated with a significant morbidity and mortality. The regulation of phosphocalcic metabolism is subject to a particularly precise and complex control of parathormone (PTH) and vitamin D. Assessment of vitamin D and parathyroid hormone concentrations would help to improve the medical management of patients with chronic kidney disease and ensure a better quality of life. **Methods**: The study population consisted of 138 individuals including 46 non-dialysis renal failure patients, 46 chronic hemodialysis patients and 46 non-renal failure volunteers to serve as controls. Serum Parathyroid hormone and Vitamin D concentrations were measured using the Vidas automated system. **Results**: 25-hydroxyvitamin D concentrations in controls (65 ± 2.41 nmol/L) and dialysis patients (70 ± 3.03 nmol/L) were significantly higher than those in CKD patients (48 ± 3.34 nmol/L). On the other hand, the mean values of Parathyroid hormone in dialysis patients (312 ± 36.22 pg/mL) and CKD patients (117 ± 10.68 pg/mL) were very high compared to that in controls (25 ± 2.34 pg/mL). **Conclusion**: Secondary hyperparathyroidism is common in renal failure. Parathyroid hormone and 25-hydroxyvitamin D assays would be adequate for better management of chronic renal failure.

Keywords

25-Hydroxyvitamin D, Chronic Renal Failure, Côte d'Ivoire, Secondary Hyperparathyroidism, Parathyroid Hormone

1. Introduction

Chronic kidney disease (CKD) remains a major public health problem world-

wide. Nearly 500 million people suffer from it and about 80% of them reside in low and middle income countries [1]. African countries are particularly affected due to the high prevalence of non-communicable diseases, such as hypertension and diabetes, but also communicable diseases, such as human immunodeficiency virus (HIV) infection, viral hepatitis B and C and glomerulonephritis [2].

In chronic renal failure, renal function deteriorates over time, with glomerular filtration rate (GFR) gradually decreasing. Irreversible damage leads to an inability of the kidneys to perform their vital functions of homeostasis, excretion and synthesis. They are responsible for numerous complications, particularly metabolic ones. Among these complications, mineral and bone metabolism abnormalities are important and accompanied by a significant morbi-mortality [3].

The regulation of phosphocalcic metabolism is subject to a particularly precise and complex control of parathyroid hormone (PTH) and vitamin D (25-hydroxyvitamin D).

Vitamin D is an important regulator of calcium and phosphate homeostasis and also has many extra-skeletal effects on the cardiovascular system, central nervous system, endocrine system, immune system, and cell differentiation and growth [4].

Stimulation of PTH secretion is characterized physiologically by reduced availability of vitamin D and decreased serum calcium. PTH stimulates calcium reabsorption at the renal tubules, calcium and phosphate resorption from bone tissue, and the synthesis of calcitriol (the most active metabolite of vitamin D), which increases intestinal calcium absorption [5]. Increased production of PTH plays a key compensatory role in restoring normal calcium and vitamin D levels [5]. Thus, the term secondary hyperparathyroidism is widely used to identify a compensatory phenomenon, the purpose of which is to correct reduced bioavailability of calcium and/or vitamin D. Secondary hyperparathyroidism appears early in renal failure and in the absence of treatment it leads in most renal failure patients to potentially serious skeletal (renal osteodystrophy) and extraskeletal (soft tissue calcifications, cardiac vessels and valves) complications [6]. In Côte d'Ivoire, little work has been done on vitamin D and parathyroid hormone despite their importance in phosphocalcic metabolism as well as in the occurrence of secondary hyperparathyroidism. Furthermore, according to Melamed, 25-hydroxyvitamin D (25(OH)D) deficiency is common in CKD, especially in non-Caucasian patients and in patients with advanced disease [7]. The objective of this study is to evaluate 25(OH)D and Parathyroid hormone concentrations in living chronic kidney disease patients in Côte d'Ivoire in order to improve their medical management.

2. Materials and Methods

2.1. Type and Study Site

This is a descriptive cross-sectional study which was carried out from December 2019 to December 2020 at the department of fundamental and medical bioche-

mistry of the Institut Pasteur of Côte d'Ivoire (IPCI). The study population consisted of 138 individuals (90 males and 48 females) aged 18 to 74 years and was distributed as follows: 46 patients with kidney failure who have never had dialysis (46 CKF patients), 46 chronic hemodialysis patients (46 dialysis patients) and 46 healthy volunteers to serve as control (46 controls).

2.2. Collection of Blood Samples

The samples were collected in various nephrology departments of hospitals in the district of Abidjan (Côte d'Ivoire), namely the National Centre for the Prevention and Treatment of Renal Failure (CNPTIR), the University Hospitals (CHU) of Cocody, Treichville and the General Hospital of Adjamé (HGA). Samples were taken by venipuncture, at the elbow fold on red tube without anticoagulant in fasting subjects for the determination of biochemical parameters (urea, creatinine, calcium, phosphorus and magnesium, parathyroid hormone and 25-hydroxyvitamin D). In chronic hemodialysis patients, the sample was taken before and after the dialysis session, with a frequency of twice a week.

2.3. Determination of Biochemical Parameters

Serum concentrations of urea, creatinine, calcium, phosphorus and magnesium were determined using the Cobas C311 Hitachi from Roche Diagnostics. The principle is based on the TRINDER reaction which is an enzymatic and colorimetric method using a chromogen. The intensity of the coloration or turbidity developed is directly proportional to the concentration of the substance being assayed [8]. The determination of PTH and 25(OH)D hormones was performed on the BioMéreux Vidas system, which is based on the ELFA (Enzyme Linked Fluorescent Assay) technology. This is an immuno-enzymological technique of detection by fluorescence carried out in two stages, which makes it possible to visualize an antigen-antibody reaction thanks to a coloured reaction produced by the action on a substrate of an enzyme previously attached to the antibody. The resulting light intensity constitutes the analytical signal which is directly proportional to the concentration of the substance measured in the sample [9].

2.4. CKD-EPI Equation

The Chronic Kidney Disease EPIdemiology collaboration (CKD-EPI) equation [10] was used to estimate the glomerular filtration rate (GFR) and thus to determine the stage of chronic kidney disease in non-dialysis patients (46 CKD patients).

2.5. Statistical Analysis

The Graph Pad Prism 8.0 software (Microsoft, USA) was used for statistical analysis. The mean values along with standard error on the mean (Mean ± SEM) of the data were calculated using analysis of variance (ANOVA) followed by Tukey's multiple comparison test. The difference is significant when p-value < 0.05.

3. Results

3.1. Epidemiological Data

This study showed a predominance of males in hemodialysis and CKD patients 30 males (65.22%) and 16 females (34.78%) with a sex ratio M/F was 1.87. The mean age for hemodialysis patients was 48 ± 1.99 and for CKD patients was 46 ± 1.86.

3.2. Stage of the Disease

The stage of chronic kidney disease was calculated in the 46 CKD patients not yet on dialysis revealed 93.48% in stage 5 and 2.18% in stage 4 against 4.34% in stage 3A.

3.3. Biochemical Profile

Compared with controls, a significant decrease in mean calcium values and a significant increase in mean phosphorus values were observed before dialysis hemodialysis patients and patients with kidney failure who have never had dialysis (CKD patients) ($P < 0.05$) (Table 1). However, hemodialysis patients after the dialysis session, showed elevated mean calcium values and lowered mean phosphorus values.

In contrast, the observed mean magnesium values were within the normal reference range with no significant difference between the different study populations (Table 1). The average values of 25(OH)D values are lowered (below 75 mmol/L) in the different study groups. The average values of 25(OH)D in CKD patients are significantly lower than those of dialysis patients and controls (Figure 1). With regard to parathyroid hormone, its concentration in CKD patients was higher than in controls and significantly lower than in dialysis patients (Figure 2).

4. Discussion

In general, chronic renal failure patients (CKD and dialysis patients) showed phosphocalcium disturbances compared to controls. The elevated parathyroid

Table 1. Average concentrations of biochemical markers in the study population.

Parameters	Control	Before dialyse	After dialyse	CKD	p value a	p value b	p value c
Creatin (5 - 12 mg/l)	9.59 ± 0.31	158.1 ± 4.5	61.04 ± 3.65	140 ± 9.23	0.0001*	0.09	0.0001*
Urea (0.10 - 0.35 g/l)	0.24 ± 0.01	1.57 ± 0.05	0.54 ± 0.04	2.13 ± 0.13	0.0001*	0.0001*	0.0001*
Calcium (90 - 110 mg/l)	90.84 ± 2.46	77.16 ± 2.36	99.81 ± 2.55	58.20 ± 4.79	0.99	0.0001*	0.0001*
Phosphorus (28 - 45 mg/l)	37.53 ± 1.75	41.38 ± 2.34	25.91 ± 2.05	60.47 ± 4.44	0.99	0.77	0.88

CKD: patients with kidney disease who have never had dialysis; Before Dialyse: chronic hemodialysis patients before the dialysis session; After Dialyse: chronic hemodialysis patients after the dialysis session. *: p indicates statistical significance. The difference is significant for $p < 0.05$. a: Control vs chronic hemodialysis patients before the dialysis session, b: Control vs chronic hemodialysis patients after the dialysis session, c: Control vs patients with kidney disease who have never had dialysis.

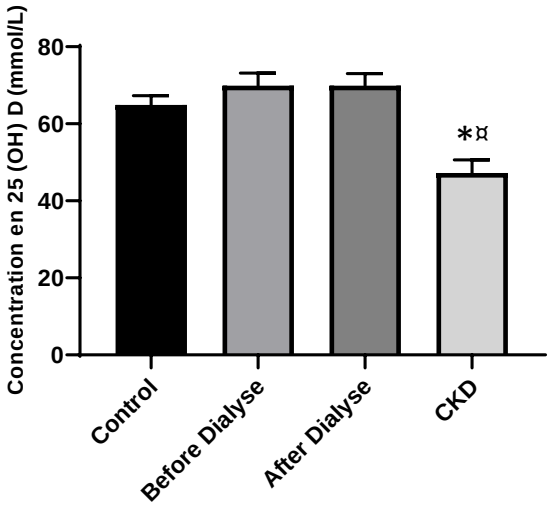

Figure 1. 25-hydroxyvitamin D concentration of the study population.

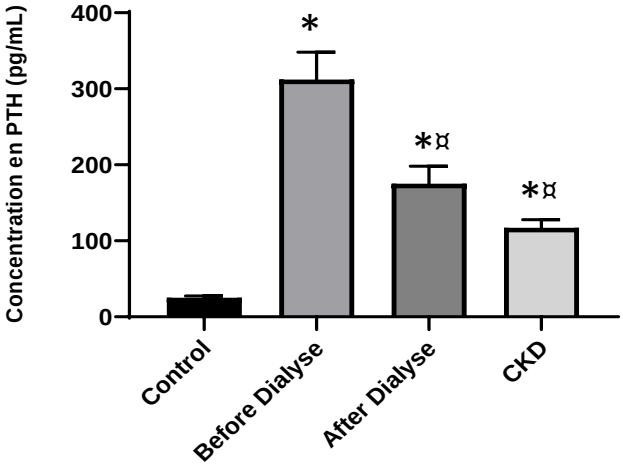

Figure 2. Parathyroid hormone concentration of the study population.

CKD: patients with kidney disease who have never had dialysis; Dialysis patients: chronic hemodialysis patients. *: Significant difference between chronic renal failure patients (CKD and dialysis patients) and controls, $P < 0.05$. ¤: Significant difference between patients before dialysis and after dialysis and CKD patients, $P < 0.05$.

hormone level, in CKD and dialysis patients is similar to the work of Mondé in renal failure patients [11]. This is indicative of hyperparathyroidism (HPT). However, the significant decrease in PTH observed during dialysis could be due not only to the decrease in its secretion induced by the hypercalcemia occurring during dialysis but also to its elimination in the dialysate [12]. Hyperparathyroidism represents one of the most common complications of CKD progression and could be explained by several interrelated mechanisms. Under hypocalcemic conditions, the percentage of intact PTH released into the bloodstream increases, and under hypercalcemic conditions, it decreases [13]. During renal failure, hypocalcemia sets in relation to reductions in renal tubular reabsorption and intestinal calcium absorption, which will directly stimulate PTH mRNA synthesis.

Indeed, parathyroid cells can sense even small changes in serum calcium levels through a membrane receptor (CaSR), resulting in changes in PTH release and synthesis [14]. Also, experimental data suggest that a reduction in CaSR expression on parathyroid cells, resulted in an increase in the set point for calcium-controlled PTH release, may contribute to increased PTH secretion during CKD [15]. A significant increase in blood calcium levels after dialysis has been observed. Since the calcium concentration in the dialysate is higher than the ionized calcium in the blood, the session allows a transfer of calcium to the patient's blood (protein-bound calcium does not diffuse). Unfortunately, there is little clinical evidence on which calcium balance should be targeted to best address potential benefits and risks for renal patients. This makes it difficult to define the optimal dialysis bath calcium concentration in each patient [16]. Furthermore, decreased renal function is also associated with hyperphosphatemia as observed in CKD patients. Phosphatemia is regulated by two proteins with a central phosphate role namely FGF23 (Fibroblast Growth Factor 23) and its co-receptor α Klotho [17]. Unfortunately, there is also a decrease in α Klotho production with the progression of chronic kidney disease; thus, the efficacy of FGF23/Klotho to correct phosphate excretion is limited, and as CKD progresses, there is the development of overt hyperphosphatemia, resulting in further stimulation of FGF23 production. In addition hyperphosphatemia directly inhibits calcium sensing receptors and also stimulates PTH production [18]. However, normal phosphatemia has been noted in dialysis patients. These results could be explained by a low phosphate diet and pharmacological interventions (the intake of phosphate binders) aimed at limiting gastrointestinal absorption [19]. Similarly dialysis favours the decrease in phosphate content in dialysis patients hence the decrease observed in the latter. The hypovitaminosis D observed in controls could be explained by an insufficient consumption of food containing or enriched in vitamin D. Indeed, circulating vitamin D has a double oringine: exogenous, dietary (ergocalciferol, cholecalciferol, present for example in certain plants or fatty fish) and endogenous by cutaneous synthesis. The main source of vitamin D is sunlight-induced skin synthesis and the second source is from diet and supplements [20]. However in blacks, skin pigmentation affects the production of vitamin D by skin synthesis. As a result, black people have lower levels of 25(OH)D, potentially due to melanin (skin pigment) acting as a natural sunscreen, leading to decreased vitamin D_3 synthesis in the skin [21]. The 25(OH) vitamin D content, although lowered in dialysis patients, is significantly higher than in CKD patients. This is due to vitamin D supplementation in dialysis patients. In renal failure, disturbances in vitamin D metabolism play a major role in the development of secondary hyperparathyroidism. Low calcidiol or 25-hydroxyvitamin D levels observed during renal failure are widespread in CKD [22]. The decrease in 1,25-dihydroxyvitamin D or calcitriol is further related to the decrease in 25-hydroxyvitamin D independently of the stage of renal failure. The hydroxylation of 25(OH) vitamin D to form $1,25(OH)_2$ vitamin D, the most active and func-

tional hormonal form of vitamin D, occurs primarily in the proximal right tubule of the kidney [23]. The enzyme responsible for the conversion of 25(OH)D to $1,25(OH)_2D$ is renal 1-α-hydroxylase (CYP27B1 Cytochrome 27 B1 mitochondrial). The decrease in 25(OH)D is thought to contribute to the decrease in $1,25(OH)_2D$ observed in advanced stages of renal failure, due to the decrease in 1-α-hydroxylase activity, but also due to the decrease in the substrate of this enzyme [24]. Calcitriol levels gradually decrease as glomerular filtration rate decreases. This decrease in calcitriol levels is due to several renal factors, such as a decrease in renal CYP27B1 with reduced renal mass; loss of renal megalin required for calcidiol uptake by the proximal tubule; and low amounts of calcidiol delivered to proximal tubular cells for activation to calcitriol [25]. In addition, regulatory factors, such as elevated FGF23 levels, which occur in early CKD, directly suppress renal CYP27B1 and exacerbate calcitriol deficiency [26]. Under normal conditions, calcitriol acts directly to decrease PTH synthesis by binding to the vitamin D receptor (VDR) in the nucleus of the parathyroid cell. Upon binding to calcitriol, the VDR, undergoes a conformational change and forms a complex with the retinoid X receptor. This VDR/retinoid X receptor complex then binds to specific sequences in the target genes and alters the rate of gene transcription; one effect is to reduce transcription of the pre-pro-PTH gene, the first step in PTH synthesis [27]. Calcitriol may also inhibit PTH indirectly by increasing intestinal calcium absorption [28]. In kidney disease, calcitriol synthesis is reduced and thus the normal endocrine feedback loop to control PTH synthesis is broken.

5. Conclusion

During renal failure, various metabolic complications develop, including secondary hyperparathyroidism. The latter is due to a set of interrelated factors, such as disturbances in phosphocalcic metabolism and a drop in 25-hydroxyvitamin D levels correlated with calcitriol levels. The control of these factors is therefore essential to mitigate the adverse effects of the disease. Also a better control of the causal affections of the renal insufficiency as well as a sensitization of the populations would support an early detection of the renal insufficiency. For a better management of renal insufficiency, it would be appropriate to make the measurements of 25-hydroxyvitamin D and parathormone.

Ethical Statement

The study was authorized for implementation by the national ethics committee for life and health sciences (CNESVS) assigned number 023-20/MSHP/CNESVS-km. Informed Consent has been obtained from the individuals for the use of blood samples for the research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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