Original Article

Parathyroid Hormone and 25(OH) Vitamin D Levels in Cameroonian Patients with Chronic Kidney Disease: A Comparison of Patients with and Without Diabetes

Taux de 25-hydoxyvitamin D3 et de parathormone chez les sujets diabétiques atteints de maladie rénale chronique : comparaison entre sujets diabétiques et non diabétiques

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ABSTRACT

Background: Chronic kidney disease (CKD) patients with diabetes show lower levels of 25-hydoxyvitamin D3 (25(OH)D) and parathormone (PTH) compared to non-diabetics in temperate climates. Our aim was to investigate if this association exists in CKD populations in tropical climates.

Methods: This cross-sectional study compared fasting serum levels of 25(OH)D and intact PTH in unselected patients with and without diabetes treated for CKD stages 3-5D in 3 nephrology facilities in Cameroon from January-March 2013. Stepwise multinomial logistic regression analysis was used to determine factors associated with 25(OH)D deficiency in non-dialyzed patients. Statistical significance was set at a P value≤0.05

Results: Of 112 patients, 45 were diabetics (24 dialyzed) and 67 non-diabetics (51 dialyzed). Diabetics were older (p<0.001), had higher BMIs (p =0.004), more males (p=0.042); received less phosphate binders (p=0.031) and more oral vitamin D3(p=0.007). Mean dialysis vintage was 39±35.6 months (n=75). Mean serum calcium, phosphorus and albumin were 9.5±0.9mg/dl, 4.7±0.23mg/dl and 3.8±0.6mg/dl respectively and comparable in the 2 groups. Diabetics had significantly lower median (25th-75th percentiles) PTH [234(124-405) *vs.* 475(219-970)pg/ml p=0.021] and 25(OH)D levels [20.2(10.4-32.8) *vs.* 28.4(20.8-42.6)ng/ml p=0.031]. Vitamin D deficiency (25(OH)D≤15ng/ml) was more prevalent in diabetics (40.0% *vs.* 14.9%, p=0.003), and this was independently associated with vitamin D deficiency in non-dialyzed patients (OR =7.51, 95%CI 1.71-33.3, p=0.007).

Conclusion: Our findings confirm reports from temperate zones and suggest a need for regular monitoring of PTH and 25(OH)D levels especially in non-dialyzed diabetics with CKD in tropical regions.

Key words: Parathormone- 25(OH)D- vitamin D deficiency- diabetes- CKD

RÉSUMÉ

Contexte: Les diabétiques atteinte de maladie rénale chronique (MRC) présentent un faible taux de 25-hydoxyvitamin D3 [25(OH)D] et parathormone (PTH) comparé aux non-diabétiques dans les régions tempérées. Le but de ce travail était de vérifier cette hypothèse dans une population similaire sous les tropiques.

Méthodes: Il s'agissait d'une étude transversale réalisée de Janvier à Mars 2013 dans 3 unités de néphrologie du Cameroun, comparant les taux sanguins de 25(OH)D et PTH chez les patients diabétiques et non-diabétiques avec une MRC stades 3-5D. Le modèle de régression logistique multinomial étés utilise pour rechercher les facteurs associé au déficit en vitamine D chez les non kit5dialysés.

Résultats: Etaient inclus 112 patients (75 hémodialysés) dont 45 diabétiques (24 hémodialysés). L'âge avancé, le sexe masculin, l'index de masse corporelle élevé, la sous- utilisation des chélateurs de phosphore et la supplémentation en vitamine D étaient associés au diabète (tous p<0,042). Les moyennes de la calcémie (9,5±0,9mg/dl), la phosphorémie (4,7±0,23mg/dl) et l'albuminémie (3,8±0,6mg/dl) étaient comparables dans les 2 groupes. La médiane (25-75 percentiles) de PTH [234(124-405) *vs.* 475(219-970)pg/ml p=0,021] et 25(OH)D [20,2(10,4-32,8) *vs.* 28,4(20,8-42,6)ng/ml p=0,031] était plus basse chez les diabétiques qui présentaient une prévalence élevée de déficit en vitamine D (40,0% *vs.* 14,9%, p=0,003). Le diabète était l'unique facteur associé au déficit en vitamine D chez les non dialysés (OR =7,51, 95%CI 1,71-33,3, p=0,007).

Conclusion: Nos résultats sont similaires aux données des régions tempérées et suggèrent une surveillance régulière des taux sanguins de PTH et 25(OH)D particulièrement chez les diabétiques non-hémodialysés sous les tropiques.

Mots clés: Parathormone - 25(OH) vitamin D - Déficit vitamine D – diabète - MRC

INTRODUCTION

Compared with non-diabetics, patients with diabetes progress faster to ESRD and show higher rates of cardiovascular disease (CVD) events and mortality despite advances in the care of diabetes and other traditional cardiovascular risk factors (1–3). Novel pathophysiologic mechanisms including the mineral bone disease (MBD) of chronic kidney disease (CKD) have been proposed as explanations for this excess morbidity. The manifestations of CKD-MBD include both 25-hydoxyvitamin D3 (25(OH)D and 1, 25 dihydroxyvitamin D deficiencies, disorders of calcium and phosphorus metabolism, secondary elevation in parathyroid hormone (PTH). fibroblast growth factor (FGF-23) (4) bone disease and extra skeletal calcifications involving the arterial system. Vitamin D deficiency especially 25(OH) D deficiency has been identified as a risk factors for ESRD, CVD and overall mortality in the CKD population (5–7). Lower levels of 25(OH) D and PTH have been reported in diabetic CKD subjects compared to their non-diabetic counterparts(8,9). However, these studies were done mainly in temperate climates where sun exposure is less, dietary habits are different and the diabetic CKD population is much older compared to ours. Moreover, PTH and vitamin D assays are not routine practice due to cost concerns in our CKD population. Our aim was therefore to determine if differences exist in serum levels of PTH, 25(OH) D and the frequency of vitamin D deficiency between patients with and without diabetes in a sunny tropical climate.

MATERIALS AND METHODS

Study population

We carried out a cross-sectional study with consecutive sampling in three reference hospitals of Cameroon (Yaoundé General Hospital, Yaoundé University Teaching Hospital and Douala General Hospital) from January to March 2013 when the average sunlight exposure per day is about 5 hours. We included adult patients with CKD stages 3 through5D aged ≥ 18 years. Patients on vitamin D therapy (native vitamin D or analogs of calcitriol), phosphate binders or calcimimetics were included. Ethical clearance for the study was obtained from the ethics committees of the different hospitals.

Procedures, assays and calculations

Relevant demographic and clinical data was collected from the medical records of consenting participants. Fasting blood samples were then collected without a tourniquet for laboratory analysis. Biochemical analysis was done in a commercial laboratory: PRIMA Ltd, Yaoundé, Cameroon. Serum calcium, phosphorus, albumin, and creatinine were assayed by routine laboratory methods on the automate Cobas c111 (Roche Diagnostics, Switzerland). Intact PTH and 25-OH vitamin D were measured on the automate Cobas e411 (*Roche Diagnostics, Switzerland)* with the kits Elecsys® PTH STAT system and Elecsys® Vitamin D Total respectively. GFR was estimated by the CKD-EPI creatinine equation(9)

Statistical analysis

The Student-t test (for normally distributed data) or Mann-Whitney U-test (for skewed data) was used for comparison of continuous variables. We compared median values of PTH and 25(OH)D between diabetics and non-diabetics using the non-parametric median test corrected for Yates continuity. Pearson χ^2 test was used to compare sub-groups for categorical variables. Stepwise multinomial logistic regression analysis, including 25(OH)D as the dependent variable were used to determine potential factors associated with 25(OH)D deficiency in non-dialyzed patients. All statistical analyses were done using SPSS 18.0 (IBM corp., Chicago, USA). Statistical significance was set at a p-value < 0.05. Descriptive statistics of continuous variables are presented as means ± standard deviation, or as medians (25th-75th percentiles). Categorical variables are expressed as distributions (frequencies, percentages). Vitamin D deficiency was defined according to KDIGO guidelines as a serum 25(OH) vitamin D level ≤ 15ng/ml(4)

RESULTS

A total of 112 patients, 45 diabetics, 67 non-diabetics) were included in the study, with 75 of them undergoing maintenance hemodialysis (CKD stage 5D).

Patient characteristics

Demographic and clinical data of the patients is shown in Table I. The diabetic sub-population was significantly older (60.2 vs. 50.5 years, p<0.001), had a higher BMI (26.4 vs. 24.0 kg/m² p =0.004), a lower mean diastolic blood pressure (p=0.015) and a higher male frequency (77.8% vs. 58.2%, p=0.042). There were significantly more diabetic patients on oral vitamin D_3 than non-diabetics (p = 0.007). For patients on hemodialysis (CKD stage 5D), the mean dialysis vintage was 39±35.6 months (range 1-83 months).

Table I. Comparison of clinical parameters in patients with and without diabetes in the study population

Characteristics	All patients	Non-diabetic	diabetic	p-value*
	n = 112	n = 67	n = 45	
Age (mean years)	54.4 ± 11.9	50.5 ± 12.7	60.2 ± 7.9	< 0.001
Male gender: n (%)	74 (66.1%)	39 (58.2%)	35 (77.8%)	0.042
CKD-MBD linked medications. n(%)				
• **Phosphate binders**	66 (58.9%)	45 (67.2%)	21 (46.7%)	0.031
• **Active vitamin D analogs**	22 (19.6%)	12 (17.9%)	10 (22.2%)	NS
• **oral vitamin D_3**	10 (8.9%)	2 (3.0%)	8 (17.8%)	0.007
Clinical parameters(mean±SD)				
• **Systolic BP**	141.2 ± 13.9	140.9 ± 11.2	141.6 ± 14.8	NS
• **Diastolic BP**	80.4 ± 10.6	82.3 ± 11.1	77.4 ± 9.1	0.015
• **BMI**	24.9 ± 4.3	24.0 ± 4.1	26.4 ± 4.3	0.004

Data are means±SD or percent. BMI: body mass index, BP: blood pressure; CKD-MBD: chronic kidney disease-mineral bone disease.
* Diabetic *versus* non-diabetic

Biochemical profile of patients with and without diabetes mellitus

Globally, apart from the mean serum creatinine which was significantly lower in diabetics, the 2 groups were comparable in terms of serum levels of calcium, phosphorus, albumin, total alkaline phosphatase, and calcium-phosphorus product (Table

II). In the non-dialyzed population, serum phosphorus and albumin were significantly lower in diabetics while serum calcium was higher (p=0.039, 0.008, 0.016 respectively) (Table III). Meanwhile, biochemical parameters were comparable between patients with and without diabetes in the dialyzed sub-population (Table IV). The median (25^{th} -75^{th} percentile) PTH and 25(OH) vitamin D levels were significantly lower in diabetics compared to their non-diabetic counterparts, 234(124-405 *vs.* 475(219-970 pg/ml (p=0.021) for intact PTH and 20.2(10.4-32.8) *vs.* 28.4(20.8-42.6)ng/ml (p=0.031) for 25(OH)D. However in subgroup analysis, PTH levels were comparable in diabetics and non-diabetics in the non-dialyzed and dialyzed sub-populations respectively (figure 1) The median(25^{th}-75^{th} percentile) level of 25(OH) D was significantly lower in diabetics in the non-dialyzed (11.3(7.05-16.1) *vs.* 24.7(15.1-32.4)ng/l p=0.014) but not in the dialyzed sub-population (figure 2). Globally, median 25(OH) vitamin D levels were higher in the dialyzed compared to the non-dialyzed population (29.7 (24-44.7) *vs*. 15.0 (8.9-25.6) ng/mL, p<0.001).Vitamin D deficiency was more prevalent in diabetic patients (40.0% vs. 14.9%, p=0.003). On multivariate analysis, diabetes was independently associated with vitamin D deficiency in the non-dialysis population (OR 7.51, 95% CI 1.71-33.3 *p* =0.007) (Table VI)

Table II: Comparison of biochemical parameters between diabetic and non-diabetic patients in study population

Analyte	All patients	Non-diabetic	diabetic	p-value*
	n = 112	n = 67	n = 45	
Creatinine (mg/dL)	8.8 ± 5.2	9.9 ± 5.1	7.2 ± 5.0	0.007
Calcium (mg/dL)	9.5 ± 0.9	9.4 ± 1.1	9.6 ± 0.7	NS
Phosphorus (mg/dL)	4.7 ± 2.3	4.9 ± 2.6	4.4 ± 1.6	NS
Ca×P (mg²/dL²)	44.5 ± 22.2	45.6 ± 25.5	42.9 ± 16.3	NS
Albumin (g/dL)	3.8 ± 0.6	3.9 ± 0.6	3.7 ± 0.6	NS
Vitamin D deficiency n(%)	28 (25)	10 (14.9)	18 (40.0)	0.003

Data are means±SD or percent. Ca×P: calcium-phosphorus product
* Diabetics *versus* non-diabetics

Table III: Comparison of biochemical parameters in non-dialyzed patients with and without diabetes.

Analyte	All patients	Non-diabetic	diabetic	p-value*
	n = 37	n = 16	n = 21	
eGFR (mL/min/1.73m²)	24.0 ± 15.7	21.5 ± 18.5	25.9 ± 13.3	NS
Calcium (mg/dL)	9.3 ± 1.1	8.7 ± 1.3	9.6 ± 0.7	0.016
Phosphorus (mg/dL)	4.2 ± 1.4	4.8 ± 1.6	3.8 ± 1.1	0.039
Ca×P (mg²/dL²)	38.4 ± 11.2	40.7 ± 11.7	36.6 ± 10.6	NS
Albumin (g/dL)	3.5 ± 0.5	3.8 ± 0.3	3.4 ± 0.5	0.008
Vitamin D deficiency n (%)	19 (51.4)	4 (25)	15 (71.4)	0.006

Data are means±SD or percent, eGFR: estimated glomerular filtration rate, Ca×P: calcium-phosphorus product
* Diabetics versus non-diabetics

Table IV: Comparison of biochemical parameters in dialyzed patients with and without diabetes.

Analyte	All patients	Non-diabetic	diabetic	p-value*
	n = 75	n = 51	n = 24	
Creatinine (mg/dL)	10.8 ± 4.5	11.1 ± 4.6	10.2 ± 4.3	NS
Calcium (mg/dL)	9.6 ± 0.8	9.6 ± 0.9	9.6 ± 0.7	NS
Phosphorus (mg/dL)	4.9 ± 2.6	4.9 ± 2.9	5.0 ± 1.8	NS
Ca×P (mg²/dL²)	47.6 ± 25.5	47.2 ± 28.4	48.3 ± 18.5	NS
Albumin (g/dL)	3.9 ± 0.7	3.9 ± 0.7	3.9 ± 0.6	NS
Vitamin D deficiency n(%)	9 (12)	6 (11.8)	3 (12.5)	NS

Data are means±SD or percent. Ca×P: calcium-phosphorus product
* Diabetic *versus* non-diabetic

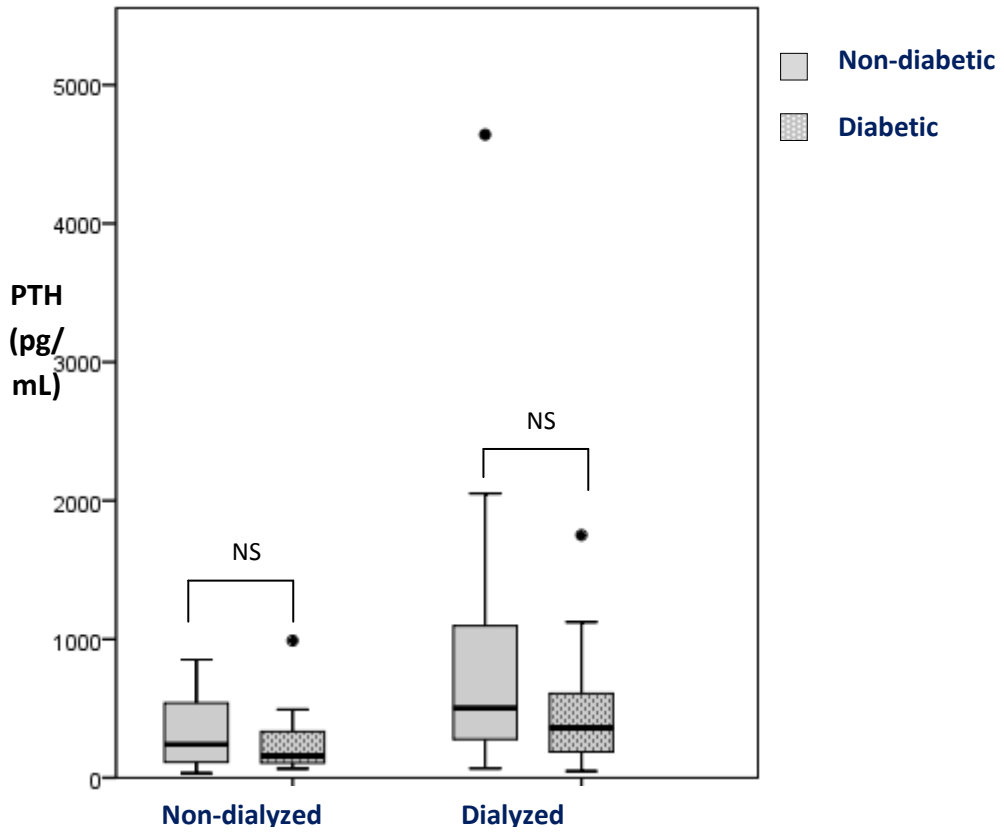

Figure 1. Comparison of median serum PTH levels in patients with and without diabetes.

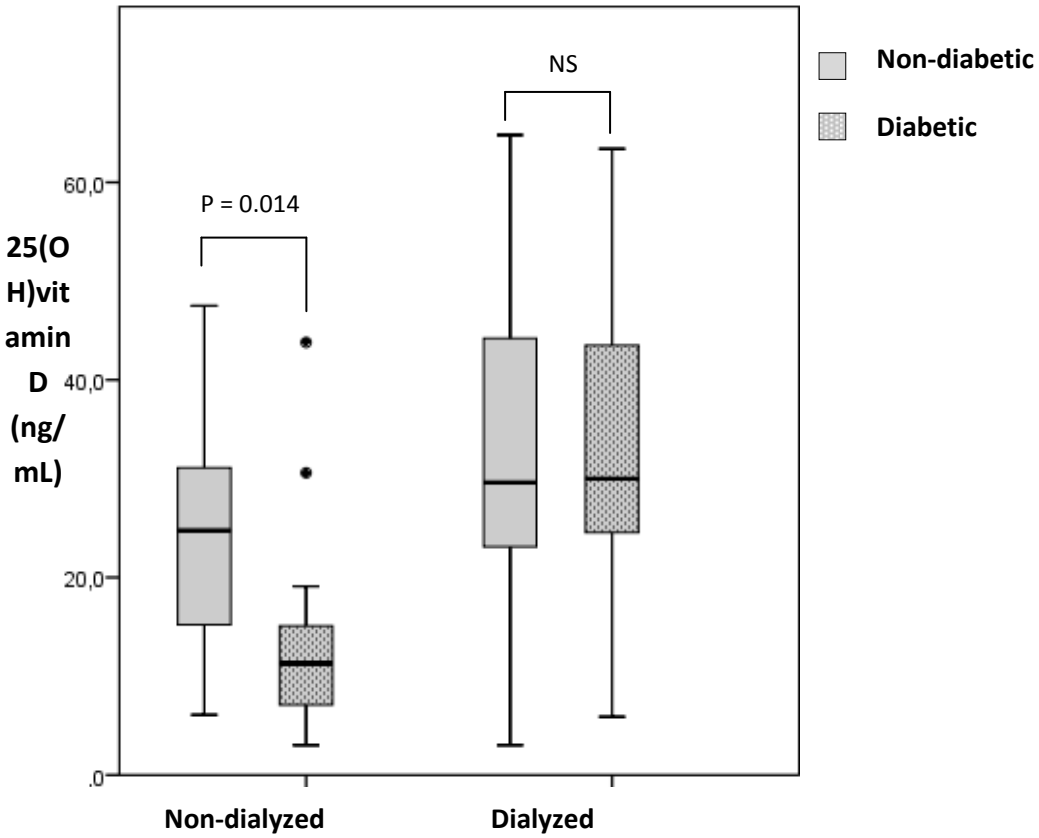

Figure 2. Comparison of median serum 25(OH) D levels in patients with and without diabetes.

Table V: Multivariate analysis: independent association with vitamin D deficiency in non-dialyzed participants.

Variable	OR	CI (95%)	p-value
Diabetes	7.51	1.71 – 33.3	0.007
BMI < 25 Kg/m²	1.28	0.20 – 7.93	NS
Calcium < 8.4 mg/dL	6.75	0.64 – 71.4	NS
Phosphorus > 4.5 mg/dL	3.07	0.39 – 24.4	NS
Albumin < 3.5 g/dL	2.20	0.38 – 12.8	NS

BMI, body mass index; CI, confidence interval; OR, odds-ratio.

DISCUSSION

We found significantly lower levels of PTH and 25(OH)D in diabetic Cameroonians with CKD compared to their non-diabetic counterparts in a population largely undertreated for CKD-MBD. However, in sub-group analysis, only vitamin D levels were significantly lower in the diabetic non-dialysis population. We observed no difference in median PTH and vitamin levels in patients with and without diabetes in the dialysis sub-population. Vitamin D deficiency was more prevalent in the diabetic non-dialysis population, whereas, the frequency of vitamin D deficiency was comparable among diabetics and non-diabetics in the dialysis sub-population. Our results are consistent with studies in temperate regions which have reported significantly lower levels of 25(OH) D in diabetics compared to non-diabetics in the pre-dialysis stages of CKD. However, in contrast to most studies, we found no difference in PTH levels between the two groups in the dialysis population.

Studies comparing PTH levels between diabetic and non-diabetic non-dialysis CKD populations in temperate countries have shown conflicting results. In consonance with the present study, some studies have found no difference in PTH levels between diabetic and non-diabetic non-dialyzed CKD populations(11,12). However others have reported lower PTH levels in non-dialyzed CKD diabetics compared to their non-diabetic counterparts(13,14). These conflicting results may reflect variations in therapeutic interventions and patient characteristics from one study to another. Our study population was largely undertreated for MBD, with only about a fifth receiving active vitamin D analogues and 60% on phosphate binders. Despite lower median PTH levels in the diabetic dialysis population, the difference did not attain statistical significance. Lower PTH levels and low turnover bone disease have consistently been reported in diabetics compared to non-diabetics on hemodialysis (8,9,14–17). The small number of diabetic patients on dialysis and the lower dialysis vintage in the present study compared to the latter studies may explain our findings. Some studies have demonstrated a direct effect of diabetes on parathyroid cells; a high glucose concentration inhibits PTH secretion(18) while diabetes triggers osteoblast refractoriness to PTH (19,20). Lower PTH levels, reduced bone formation rates, decreased bone mass and greater risk of fractures have also been reported in patients with diabetes and normal renal function compared to those without diabetes(21,22)

We observed significantly lower vitamin D levels and a higher prevalence of vitamin D deficiency in diabetics despite a significantly more frequent use of native vitamin D3. The association of diabetes with lower levels of 25(OH) D and vitamin D deficiency is consistent with other reports that have shown lower levels of vitamin D levels and a higher frequency of vitamin D deficiency in non-dialyzed CKD patients with compared to those without diabetes (12,13,23,24). Nevertheless and contrary to some reports, we found no difference in vitamin D levels between diabetic and non-diabetic participants in the dialyzed sub-population (25,26). The lower serum albumin concentration in the non-dialyzed population in the present study which may reflect higher urinary protein loss in that group, may account for the difference in 25(OH) D levels between the sub-populations. Although not evaluated in the present study, proteinuria is a major feature of diabetic kidney disease and may thus explain the lower serum albumin levels in diabetics. In CKD populations, serum albumin positively correlates with vitamin D levels (12,27) while proteinuria is negatively associated with 25(OH) D levels through excretion of the 25(OH)–vitamin D-binding protein complex(28,29). The progressive decrease in urine output that occurs on maintenance hemodialysis is accompanied by a decrease in urinary protein loss and increase serum albumin thus increasing 25(OH) D levels in the dialysis subgroup. Some factors such as a higher BMI, higher calcium, older age seen in the diabetic population can explain the lower 25(OH)D levels; conversely the lower PTH, more frequent use of oral native vitamin D3 in diabetics in general, and the higher glomerular filtration rate in the non-dialyzed diabetic group favor increases in 25(OH)D level(27,30,31). On multivariate analysis however, diabetes was associated with vitamin D deficiency independent of BMI, serum calcium, albumin and phosphorus in the non-dialysis population (OR 7.51, 95% CI 1.71-33.3 p =0.007). Vitamin D deficiency has been shown to increase the risk of insulin resistance and consequently diabetes(32,33)

The main limitation of the study is its cross-sectional design, which does not permit temporal causal relationships or strength of association between diabetes and studied variables. Furthermore, the study is underpowered due to its small sample size. Despite these limitations we were able to show a high prevalence of vitamin D deficiency in patients with CKD and

significant differences in 25(OH) vitamin D levels and deficiency in CKD patients with and without diabetes living in a tropical sub-Saharan African country.

Our findings are consistent with reports from temperate zones and suggest a need for regular monitoring of PTH and 25(OH) D especially in non-dialyzed diabetics with CKD in tropical sunny areas. More powered studies are needed to confirm these findings and assess the impact of these abnormalities on patient outcomes.

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