COMPARATIVE STUDY OF VITAMIN D AMONG DIABETIC AND NONDIABETIC CHRONIC KIDNEY DISEASE PATIENTS

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Abstract

Background: Chronic Kidney Disease (CKD) is a major health problem in Bangladesh. Diabetes mellitus is the most common cause of this pathology. Among individuals with CKD, vitamin D deficiency is very much prevalent. But there are not enough studies comparing vitamin D status of diabetic and nondiabetic CKD patients. So, this study aimed to compare the 25(OH)D levels between these two groups.

Materials and methods: This cross-sectional comparative study was carried out in the Department of Biochemistry and the Department of Nephrology, Chittagong Medical College Hospital from June 2013 to May 2014. Fifty (50) diabetic CKD patients and fifty (50) age-sex matched nondiabetic CKD patients of 18-85 years fulfilling the required enrolment criteria were purposively selected to form two comparing groups. Patient-profiles were completed by history and physical examination. Anthropometric and clinical parameters were analysed along with fasting and 2 hours after breakfast plasma glucose, serum creatinine, eGFR, serum calcium, serum phosphate and 25(OH)D. Data were analysed by computer-based statistical software. The confidence level was fixed at 95% and p-value of <0.05 was considered significant.

Results: In the study, all patients in both groups had hypovitaminosis D and the vitamin D deficiencies in diabetic and nondiabetic CKD patients were 100% and 84% respectively. Mean 25(OH)D was significantly lower in the diabetic group (5.48 ± 0.39 ng/mL) compared to nondiabetic one (9.08 ± 0.75 ng/mL), but the severity of vitamin D deficiency did not seem to correlate with CKD stages.

Conclusion: In conclusion, this study establishes the high prevalence of vitamin D deficiency in both diabetic and nondiabetic CKD patients, but the deficiency was more severe in diabetic ones.

Key words
Vitamin D; Chronic kidney disease; Diabetic CKD; Nondiabetic CKD.

Introduction

Vitamin D is a key regulator of calcium and phosphate homeostasis. An adequate amount of vitamin D is essential for optimal bone health as well as for widespread biological processes of many tissues. Vitamin D is a pro-hormone that needs to be activated for its desired effects by 25-hydroxylation in the liver to produce 25(OH)D and then 1 α-hydroxylation in kidney and extrarenal tissues to produce more active $1,25(OH)_2D$ or calcitriol. Contrary to previous belief, both 25(OH)D and $1,25(OH)_2D$ can bind to vitamin D receptor to generate a biological response[1]. 25(OH)D is the main circulating form of vitamin D and is routinely measured to evaluate vitamin D status. Amongst individuals with CKD, vitamin D deficiency is very common with prevalence as high as 80% or more in some studies[2-4]. Although this varies according to the stage of CKD, its underlying pathology, studied population and other factors. Alongside the negative impact on muscle and bone, vitamin D deficiency in CKD adversely affects endothelial function, renin-angiotensin-aldosterone system, inflammation and immunity[5-6]. It is also thought to complicate CKD and increase all-cause mortality[7-8]. Yet, there are not enough data about the vitamin D status of our diabetic or nondiabetic CKD population. So, this study aimed to compare the levels of 25(OH)D between diabetic and nondiabetic CKD patients that may give the physicians a better idea necessary to justify vitamin D supplementation and its adequate dosing.

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Materials and method

This cross-sectional comparative study was carried out in the Department of Biochemistry and the Department of Nephrology of Chittagong Medical College Hospital from June 2013 to May 2014. After taking proper permission from the concerned departments and ethical review committee, a total of 100 individuals fulfilling the required enrolment criteria were selected by purposive sampling. Of them, fifty (50) were diabetic CKD patients and fifty (50) were age-sex matched nondiabetic CKD patients.

Inclusion criteria: Subjects of 18-85 years presenting with diabetic or nondiabetic chronic kidney disease in the Department of Nephrology, Chittagong Medical College Hospital.

Exclusion criteria: Patients on dialysis or renal replacement therapy, with acute renal failure, chronic liver disease, malabsorption syndrome, granulomatous disease, on medications known to affect vitamin D absorption or metabolism such as anticonvulsants and anti-cancer drugs, isoniazid, rifampicin, theophylline, glucocorticoids, calcium and vitamin D supplements.

Informed, written consent was taken from all the participants. Patient-profiles were completed by relevant history, physical examination and anthropometric measurements. Plasma glucose, serum creatinine, serum calcium, serum phosphate and urinary albumin were estimated in an automated analyser (Siemens Dimension clinical chemistry system). eGFR was calculated by MDRD formula. Serum 25(OH)D levels were estimated by ELISA that utilizes a competitive protein binding assay. Optimal level of vitamin D was > 30 ng/mL, insufficiency 15-30 ng/mL and deficiency < 15 ng/mL. Data were analysed using computer-based statistical software. Continuous data were expressed as mean ± SEM and categorical data as frequency and percentage. The confidence level was fixed at 95% and p-value of < 0.05 was considered significant.

Results

Table I : Distribution of CKD stages among the study groups (n = 100).

CKD Stages	Study Groups				Total	
	Diabetic CKD		Nondiabetic CKD			
	n	%	n	%	n	%
Stage 3	5	10.0	9	18.0	14	14.0
Stage 4	9	18.0	5	10.0	14	14.0
Stage 5	36	72.0	36	72.0	72	72.0
Total	50	100.0	50	100.0	100	100.0

$\chi^2 = 2.286$, p = 0.319 (Not significant)

Table shows that there was no significant difference between the groups in stage-wise distribution of cases.

Table II: Characteristics of diabetic and nondiabetic CKD patients, (Mean ± SEM) where applicable.

Traits	Diabetic CKD n = 50	Nondiabetic CKD n = 50	p value
BMI (kg/m^2)	24.00 ± 0.47	22.61 ± 0.48	<0.05
Duration of CKD	< 5 years 86%	< 5 years 94%	
	≥ 5 years 14%	≥ 5 years 06%	>0.05
Duration of CKD (Years)	2.16 ± 0.33	1.48 ± 0.26	>0.05
Systolic BP (mm Hg)	134.00 ± 1.85	128.60 ± 1.46	<0.05
Diastolic BP (mm Hg)	83.70 ± 1.39	81.90 ± 0.84	>0.05
Haemoglobin (g/dL)	8.82 ± 0.25	8.79 ± 0.36	>0.05
FPG (mmol/L)	143.34 ± 7.93	90.80 ± 8.06	<0.05
2-hr ABF PG (mmol/L)	195.00 ± 10.60	112.67 ± 7.05	<0.05
Creatinine (mg/dL)	8.78 ± 0.69	8.59 ± 0.74	>0.05
eGFR (mL/min)	9.37 ± 1.17	13.60 ± 1.71	<0.05
Vitamin D (ng/mL)	5.48 ± 0.39	9.08 ± 0.75	<0.001
Hypovitaminosis D (%)	100	100	>0.05
Calcium (mg/dL)	7.49 ± 0.21	8.17 ± 0.28	>0.05
Phosphate (mg/dL)	6.95 ± 0.35	6.44 ± 0.24	>0.05
Urine albumin (g/day)	1.73 ± 0.17	1.37 ± 0.15	>0.05

As seen on the above table, mean Vitamin D was significantly lower in diabetic CKD group compared to nondiabetic one. eGFR was also slightly lower in diabetic individuals. On the contrary, BMI, systolic blood pressure and plasma glucose were also higher in diabetic subjects, but other parameters were not significantly different.

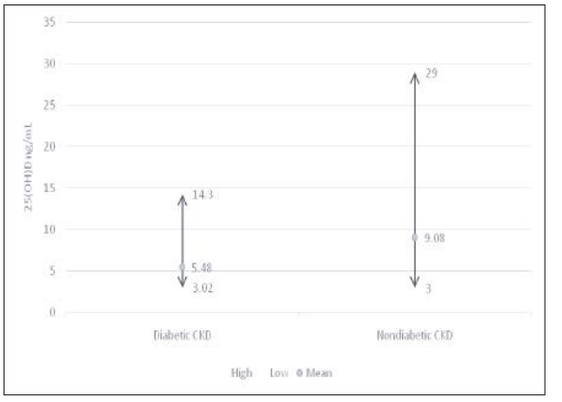

Fig 1: Stock diagram showing mean values of vitamin D (With ranges) amongst study groups.

Table III : Distribution of serum vitamin D levels into different stages (With ANOVA test of significance), n = 100.

	Study Groups	CKD stages	N	Mean	SEM	p value
Serum Vitamin D (ng/mL)	CKD	Stage 3	14	7.63	0.64	<0.001
		Stage 4	14	5.42	0.32	(Highly
		Stage 5	72	7.57	0.58	significant)
		Total	100	7.28	0.46	
	Diabetic CKD	Stage 3	05	5.45	0.35	0.789
		Stage 4	09	4.90	0.22	(Not
		Stage 5	36	5.62	0.40	significant)
		Total	50	5.48	0.39	
	Nondiabetic CKD	Stage 3	09	8.83	2.69	0.467
		Stage 4	05	6.36	0.95	(Not
		Stage 5	36	9.52	0.80	significant)
		Total	50	9.08	0.75	

In the total CKD population, there was significant difference of mean vitamin D levels among the three CKD stages. But intragroup analysis did not find similar difference. Also, mean vitamin D levels did not seem to correlate with CKD stages.

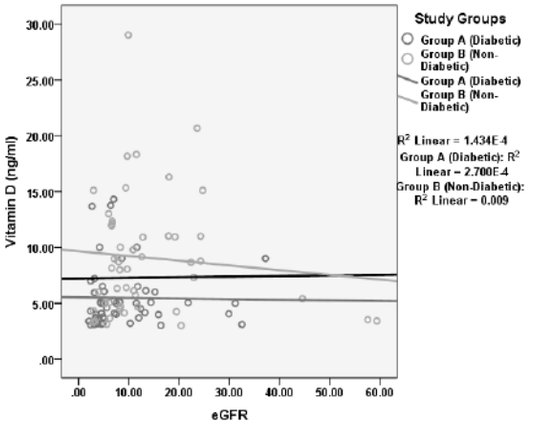

Fig 2: Scatter diagram showing insignificant correlation between eGFR and vitamin D level.

Table IV : Association between vitamin D deficiency and diabetes in CKD patients (n = 100).

Low serum vitamin D (Hypovitaminosis D) status	Study Groups				Total	
	Diabetic CKD		Nondiabetic CKD			
	n	%	n	%	n	%
Vitamin D insufficiency (15 – 30 ng/mL)	00	0.0	08	16.0	08	8.0
Vitamin D deficiency (< 15 ng/mL)	50	100.0	42	84.0	92	92.0
Total	50	100.0	50	100.0	100	100.0

χ^2 value = 8.696, p < 0.01 (Highly significant)

Table shows that all the subjects (100%) with diabetic CKD were vitamin D deficient. While vitamin D deficiency was 84% in nondiabetic CKD group. Thus, compared to nondiabetic CKD, diabetic CKD had increased association with vitamin D deficiency.

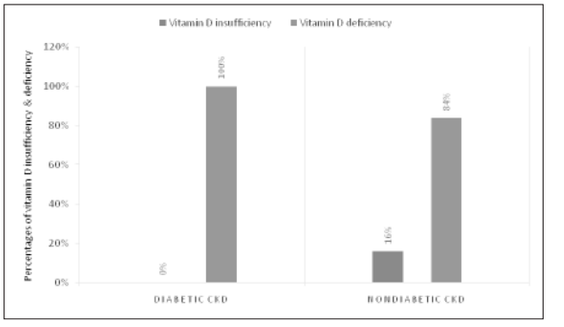

Fig 3 : Bar diagram showing distribution of hypovitaminosis D among the study groups.

Discussion

In the present study, diabetic and nondiabetic CKD patients were evenly matched in terms of age and sex proportions. Besides, there was no significant difference between the groups in the stage-wise distribution of cases. In both groups, the majority of the patients (72% in each) were in stage 5 (Table I). Comparison of anthropometric, clinical and biochemical parameters (Table II) shows that mean BMI, systolic blood pressure and plasma glucose were higher in diabetic CKD group. Differences in BMI is important because increased BMI and obesity have been implicated with hypovitaminosis D. Obesity reduces the availability of Vitamin D by sequestration in body fat[9]. As seen in results, the mean eGFR was slightly lower in the diabetic group. Other parameters were not significantly different between the groups excepting vitamin D, which was significantly lower in diabetic CKD patients (5.48 ± 0.39 ng/mL) compared to nondiabetic ones (9.08 ± 0.75 ng/mL) (Table II, Figure 1). Vitamin D levels, however, did not seem to correlate with CKD stages (Table III). Similarly, there was no significant correlation between eGFR and vitamin D level (Figure 2). Here, all patients in both groups had hypovitaminosis D (Table II). Percentage of patients with vitamin D deficiency in diabetic CKD group was 100% as opposed to 84% in the nondiabetic CKD group (Table IV, Figure 3). Thus, compared to nondiabetic CKD, diabetic CKD had increased association with vitamin D deficiency.

Similar to this study, the reported prevalence of hypovitaminosis D is consistently and unexpectedly high in almost all CKD populations studied worldwide[2-4]. In one study in chronic kidney disease patients, all the CKD patients were Vitamin D deficient[2]. The same study had found a significant difference in serum Vitamin D between diabetic (8.16 ± 3.79 ng/mL) and nondiabetic (12.45 ± 3.04 ng/mL) CKD patients. Another study comparing diabetic & nondiabetic chronic kidney disease patients concluded that diabetes is an independent predictor of Vitamin D deficiency[4]. Incipient data are showing vitamin D deficiency to be a contributing factor for the development of both type 1 and 2 diabetes which might suggest a link between the high prevalence of hypovitaminosis D and diabetes mellitus in Bangladeshi population[10-11]. The β cells of the pancreas not only secrete insulin but also contain vitamin D receptors (VDRs) and 1 α-hydroxylase enzyme[12-13]. Besides, there is evidence that treatment with vitamin D may improve glucose tolerance and insulin resistance[14].

In chronic kidney disease, decreased functional renal mass, accumulation of various metabolites like phosphates and uremic toxins reduce the activity of renal 1 α-hydroxylase enzyme resulting in low levels of calcitriol. But in CKD, there is also a deficiency of 25(OH)D. Factors contributing to reduced 25(OH)D in CKD are limited sunlight exposure, uraemia (Reduces response to UV-B irradiation) hyperpigmentation (Common in patients undergoing haemodialysis) nutritional deficiency (Low food intake due to reduced appetite, uraemia-related gastrointestinal symptoms, dietary restrictions) and impaired vitamin D absorption (Due to uraemia and other causes)[15-19]. Proteinuria has also been described as a contributing factor in vitamin D deficiency in patients with CKD[19-20]. Urinary excretion of proteins like megalin and cubilin decreases megalin and cubilin mediated reabsorption of 25(OH)D and its binding protein in proximal tubule with their loss in urine[20]. Increased shedding of megalin and cubilin have been reported in diabetes and IgA nephropathy which may explain greater deficiency of vitamin D in diabetic CKD patients[20-21]. The loss of both 25(OH)D and vitamin D binding protein through peritoneal effluent is also a well-known cause of vitamin D deficiency in patients on peritoneal dialysis.

In patients with CKD, vitamin D deficiency had been associated with high PTH, increased bone turnover and decreased Bone Mineral Density (BMD) muscle weakness, risk of falls and fractures, albuminuria, rapid progression of renal disease and increased mortality[7-8, 22-24]. Although the possible advantages of Vit D supplementation in CKD are not well-defined, initial studies reported high levels of vitamin D and a reduction in PTH[25-26]. Besides, there is evidence that the pleiotropic effects of vitamin D may transcend bone and mineral metabolism, thereby influencing other potential areas of chronic kidney disease. Recent studies indicate that vitamin D supplementation has an antiproteinuric effect and a role on the renin-angiotensin-aldosterone system[6, 27]. It may also lessen the histological changes of glomerulosclerosis and subsequently, chronic kidney disease progression. Currently, both the KDOQI & KDIGO recommends screening and supplementation for low vitamin D in CKD patients. Given the low-cost and high safety profile, patients with CKD might benefit from 25(OH)D supplementation in the setting of vitamin D deficiency and insufficiency.

Limitation

There are several limitations that might have affected our study. Some of which include single-centre cross-sectional data, small number of subjects especially in stage 3/4 of CKD, the purposive method of sampling, and single measurement of parameters.

Conclusion

In summary, vitamin D deficiency was exceedingly common in both diabetic and nondiabetic CKD patients of our investigation. Even though the deficiency was more severe in diabetic CKD patients, both groups may benefit from vitamin D screening and its supplementation according to current guidelines.

Recommendation

The extensiveness of vitamin D deficiency in both diabetic and nondiabetic CKD patients demands special attention from local researchers and clinicians. We recommend larger studies with more representative samples across all stages of CKD to better validate our findings before moving on to vitamin D supplementation trials.

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Contribution of authors
FA-Conception, design, acquisition of data, manuscript writing and final approval.

PB-Analysis, interpretation of data, manuscript writing, critical revision and final approval.

MH-Interpretation of data, critical revision and final approval.

AAMRU-Analysis of data, critical revision and final approval.

AED-Conception, design, critical revision and final approval.

Disclosure
All the authors declared no competing interests.

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