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Impact of Serum 25-Hydroxyvitamin D Deficiency on Arterial Stiffness in Non-Dialysis CKD Patients

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Abstract

Introduction: Chronic Kidney Disease (CKD) is a major global health issue, with an increasing prevalence in Bangladesh. It is associated with numerous complications, especially cardiovascular diseases, which are the leading cause of morbidity and mortality among CKD patients. Arterial stiffness, a key cardiovascular risk factor, has been shown to correlate with CKD progression. Recent studies suggest that serum 25-hydroxyvitamin D (25(OH)D) deficiency plays a significant role in the development of arterial stiffness and cardiovascular complications in CKD patients. ***Objective:*** This study aims to investigate the impact of serum 25-hydroxyvitamin D deficiency on arterial stiffness in non-dialysis CKD patients in Bangladesh. ***Methods:*** A cross-sectional observational study was conducted at the Department of Nephrology, Dhaka Medical College, between September 2021 and March 2023. A total of 100 non-dialysis CKD patients (Stages 3-5) were enrolled, with 50 patients each in the vitamin D deficient and non-deficient groups. Arterial stiffness was measured using established methods, and serum 25(OH)D levels were assessed. Statistical analysis was performed using SPSS version 26.0, with significance set at $p<0.05$. ***Results:*** The study found that 78% of patients in the vitamin D deficient group were in Stage 5 CKD, compared to 12% in the non-deficient group. A significant negative correlation was observed between serum 25(OH)D levels and arterial stiffness ($r = -0.386$, $p = 0.001$). Laboratory variables such as eGFR and hemoglobin levels were significantly lower in the vitamin D deficient group ($p<0.05$). ***Conclusion:*** The study concludes that vitamin D deficiency plays a critical role in the pathogenesis of arterial stiffness in CKD patients. Addressing vitamin D deficiency may offer potential benefits in mitigating cardiovascular complications and improving the prognosis of CKD patients in Bangladesh.

Keywords: Chronic Kidney Disease, 25-hydroxyvitamin D, Arterial Stiffness.

INTRODUCTION

Chronic Kidney Disease (CKD) is a global health issue that disproportionately affects populations across various regions, including Bangladesh, with an increasing prevalence. The disease is characterized by a gradual decline in kidney function, leading to a host of complications such as cardiovascular diseases, which are the leading cause of morbidity and mortality among CKD patients. Among the various risk factors contributing to the cardiovascular burden in CKD, arterial stiffness has been identified as a significant predictor of adverse outcomes. Arterial stiffness, a condition characterized by the reduced elasticity of the arteries, has been shown to correlate strongly with cardiovascular events such as hypertension, stroke, and heart failure [1-3].

One emerging factor influencing arterial stiffness in CKD patients is the deficiency of serum 25-hydroxyvitamin D (25(OH)D), a marker of vitamin D status in the body. Vitamin D deficiency has been widely reported to be prevalent among individuals with CKD, and recent studies have indicated its potential role in the

pathogenesis of cardiovascular diseases, particularly arterial stiffness [4-7]. Vitamin D plays a crucial role in regulating calcium-phosphate balance, immune function, and vascular health. Deficient levels of vitamin D may exacerbate vascular calcification, endothelial dysfunction, and increased vascular tone, contributing to heightened arterial stiffness in CKD patients [9-12].

In Bangladesh, the burden of CKD is on the rise, with a growing number of individuals diagnosed at various stages of the disease. Unfortunately, vitamin D deficiency remains a significant public health concern in the country, attributed to limited sunlight exposure, dietary habits, and low awareness of the importance of vitamin D in maintaining overall health. As a result, the interplay between vitamin D deficiency and cardiovascular risk in CKD patients in Bangladesh remains underexplored, particularly with regard to arterial stiffness.

This study aims to investigate the impact of serum 25-hydroxyvitamin D deficiency on arterial stiffness among non-dialysis CKD patients in Bangladesh. Understanding this relationship is essential, as it could provide valuable insights into the mechanisms underlying cardiovascular complications in CKD patients and contribute to the development of targeted interventions for managing both CKD and associated cardiovascular risks. Additionally, it could offer important public health implications for improving vitamin D status among CKD patients in Bangladesh and reducing the associated risks of arterial stiffness.

OBJECTIVE

The primary focus of this research is to evaluate the serum 25-hydroxyvitamin D levels in non-dialysis CKD patients at stages 3 to 5 and examine their correlation with arterial stiffness.

METHOD

This research utilized a cross-sectional observational design to explore the relationship between serum vitamin D levels and arterial stiffness in non-dialytic Chronic Kidney Disease (CKD) patients, specifically those in stages 3-5. The study was conducted at the Department of Nephrology, Dhaka Medical College, between September 2021 and March 2023. The study sample consisted of 100 patients, with 50 in each group, calculated using sample size estimation.

Selection Criteria

Inclusion Criteria

- Non-dialytic Chronic Kidney Disease (stages 3-5)

Exclusion Criteria

- Age < 18 years
- Primary hyperparathyroid diseases
- Malignancy
- Peripheral vascular diseases
- Chronic liver disease (CLD)

Before the commencement of the study, ethical approvals were obtained from both the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of Dhaka Medical College. Patients were selected based on the inclusion and exclusion criteria, and written informed consent was obtained from all participants. A thorough medical history and physical examination were performed, and relevant clinical and laboratory data were recorded.

The study enrolled 100 patients through purposive sampling. Each participant was informed about the study's objectives, procedures, and any potential benefits or risks. It was clarified that the study did not involve any experimental drugs or additional risks. The collected data was handled with strict confidentiality.

Data was gathered from patients with non-dialytic CKD (stages 3-5) at the Department of Nephrology, Dhaka Medical College. The inclusion and exclusion criteria were followed for patient selection, and written informed consent was secured from each participant. Information on sociodemographic factors, clinical parameters, and laboratory test results were meticulously recorded.

Following data collection, the information was reviewed for completeness, accuracy, and consistency. Descriptive statistics were applied to analyze the demographic and clinical characteristics. SPSS version 26.0 was used for data analysis, and statistical tests such as Student's t-test, ANOVA, and Chi-square were applied to compare continuous and categorical variables. A p-value of <0.05 was considered statistically significant.

The study received approval from the Ethical Review Committee (ERC) of Dhaka Medical College. Participants were informed of the study's goals and procedures, and written consent was obtained. Patient confidentiality was maintained throughout the study, and participants were reminded of their right to withdraw at any time.

RESULTS

Table I shows the demographic variables in study groups. It was observed that almost half (44.0%) of patients belonged to age ≥60 years in Vitamin-D deficient and 21 (44.0%) of patients belonged to age <40 years in Vitamin-D non deficient. The mean age was 55.35±16.79 years in Vitamin-D deficient and 43.06±16.44 years in Vitamin-D non deficient. More than half (56.0%0 of patients were male in Vitamin-D deficient and 26(52.0%) in Vitamin-D non deficient. More than one fourth (28.0%) of patients were smoker in Vitamin-D deficient and 12(24.0%) in Vitamin-D non deficient.

Table I: Demographic variables in study groups (N=100)

Demographic variables	Vitamin-D Deficient (n=50)		Vitamin-D Non-deficient (n=50)		P-value
	n	(%)	n	(%)	
Age in years					
<40	8	16.0	21	42.0	
40-49	10	20.0	10	20.0	
50-59	10	20.0	10	20.0	
≥60	22	44.0	9	18.0	
Mean± SD	55.35±16.79		43.06±16.44		[a]0.001[s]
Range (Min-Max)	19-80		15-76		
Sex					
Male	28	56.0	26	52.0	[b]0.688[ns]
Female	22	44.0	24	48.0	

The mean e GFR was 12.53±6.3 in Vitamin-D deficient and 29.42±14.07 in Vitamin-D non deficient group. The mean Hb % was 10.2±2.4 in Vitamin-D deficient and 11.1±3.2 in Vitamin-D non deficient group. The differences of Laboratory variable were statistically significant (p<0.05) between Vitamin-D deficient and non-deficient.

Table II: Laboratory variables in study groups (N=100)

Laboratory variables	Vitamin-D Deficient (n=50)	Vitamin-D Non-deficient (n=50)	P-value
	Mean± SD	Mean± SD	
e GFR	12.53±6.3	29.42±14.07	0.001[s]
Hb %	10.2±2.4	11.1±3.2	0.002[s]

s=significant
p value reached from Unpaired-t test

Table III shows the assessment according to cause of CKD. It was observed that DM, HTN, GN and others were not significantly (p>0.05) associated with Vitamin-D deficient and non deficient group.

Table III: Distribution of the study population according to cause of CKD (N=100)

Cause of CKD	Vitamin-D Deficient (n=50)		Vitamin-D Non-deficient (n=50)		P-value
	n	(%)	n	(%)	
DM	18	36.0	10	20.0	0.074[ns]
HTN	15	30.0	12	24.0	0.499[ns]
GN	12	24.0	15	30.0	0.499[ns]
Others	5	10.0	13	24.0	0.062[ns]

Table IV shows the according to CKD stage with vit-D status. It was observed that more than three fourth (78.0%) of patients had stage 5 CKD in Vitamin-D deficient and 6(12.0%) in Vitamin-D non deficient. The differences of CKD stage was statistically significant (p<0.05) between Vitamin-D deficient and non deficient.

Table IV: Comparison of vit-D status according to stages of CKD (N=100)

CKD (Stage)	Vitamin-D Deficient (n=50)		Vitamin-D Non-deficient (n=50)		P-value
	n	(%)	n	(%)	
3A	2	4.0	13	26.0	0.001[s]
3B	2	4.0	11	22.0	
4	7	14.0	20	40.0	
5	39	78.0	6	12.0	

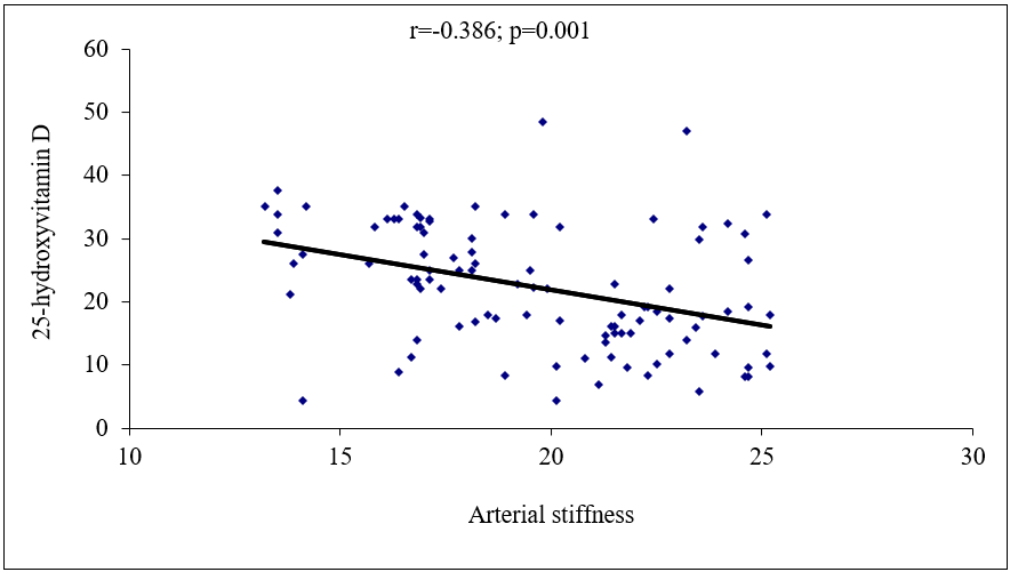

Figure 1: Scatter diagram shows the negative significant (r=-0.386; p=0.001) Pearson correlation between arterial stiffness with 25-hydroxyvitamin D

DISCUSSION

In this study, regarding the laboratory variable in study groups, the mean e GFR was 12.53±6.3 in vitamin-D deficient and 29.42±14.07 in vitamin-D non deficient group. The mean Hb % was 10.2±2.4 in Vitamin-D deficient and 11.1±3.2 in Vitamin-D non deficient group. The differences of laboratory variable were statistically significant between Vitamin-D deficient and non-deficient groups. Similar findings were observed by Lee *et al.,* (2015) [1]. Where they observed that the mean eGFR (ml/min per 1.73m2) was 56± 47 in Vitamin-D deficient group and 75±43 in vitamin-D non deficient group. The mean hemoglobin (g/l) was 114±26 in vitamin-D deficient group and 121±30 in vitamin-D non deficient group. The similar kind of study done by, Akdam H and Alp A (2017) reported that hemoglobin and eGFR were significantly lower in vitamin-D deficient group which is consistent with our study [2]. This may be due to Vitamin D deficiency is associated with cardiovascular disease and rapid decline of eGFR in patients with CKD (Nakashima A *et al.,* 2016) [3]. Also Vitamin D deficiency is associated with low eGFR, which is due to many factors such as decreased vitamin D-binding protein, proteinuria, reduced dietary intake, advanced age, malabsorption, reduced sun exposure and exercise and down-regulation of megalin levels (Nakashima *et al.,* 2016) [3]. Study conducted by Kim SG *et al.,* (2018) reported that the mean eGFR was 89.78 ± 17.01 ml/min/1.73 m2 in subjects with vitamin D sufficiency which is not consistent with our study [4]. Low level of vitamin D is associated with anaemia is likely due to chronic inflammation, in which the underlying mechanism involves, the direct suppression of hepcidine mRNA expression by vitamin D as well as the reduction of hepcidine stimulatory pro-inflammatory cytokines (John J *et al.,* 2009) [5].

In this study, regarding the assessment according to cause of CKD, it was observed that obstructive uropathy was significantly associated with Vitamin-D deficient and non-deficient. But DM, HTN, GN and others were not significantly associated with Vitamin-D deficient and non-deficient which is consistent with the study done by Akdam H and Alp A (2017), [2] the patients were divided in two groups according to their vitamin D levels. They reported that the causes of kidney disease in group I and group II were diabetes mellitus, hypertension and glomerulonephritis respectively. There is similarity to the findings of previous study that reported DM, HTN and GN as the most common etiology of CKD (Zhang *et al.,* 2018). Similarly, in a study of 633 patients in Iran, DM and HTN were reported as the most common cause of CKD (Malekmakan *et al.,* 2009) [6].

In this study, it was observed that more than three fourth (78.0%) of patients had 5 stage CKD in Vitamin-D deficient and 6 (12.0%) in Vitamin-D non deficient. The differences of CKD stage was statistically significant between Vitamin-D deficient and non-deficient. It also showed that level of vitamin D decreases as stage of CKD increase. Similar kind of result shown in stydy conducted by Akdam H and Alp A (2017) [2]. They showed that levels of 25(OH)D is decrease as stage of CKD increase. Decreased levels were observed in all CKD stages, with a tendency to decrease as the CKD stage increased. This is because serum 25(OH)D deficiency is often common in the chronic kidney disease (CKD) patients, especially in the advanced stage of CKD. There is also many factors such as decreased vitamin D-binding protein, reduced dietary intake, advanced age, malabsorption, reduced sun exposure and exercise and down-regulation of megalin levels all contribute to decrease level of vitamin D (Nakashima *et al.,* 2016) [3].

In this study, the scatter diagram showed that the negative significant Pearson correlation between arterial stiffness with 25-hydroxyvitamin D. Which is consistent with the study done by Akdam H and Alp A (2017) [2]. It showed that the marker of arterial stiffness was higher with 25(OH)D deficiency and negatively correlated with 25(OH)D. Which is because, 25(OH)D deficiency may be a contributing factor in the development of arterial stiffness in CKD and vitamin D has a beneficial impact on the renin-angiotensin system, endothelium mediated vasodilatation, insulin resistance, inhibition of vascular smooth muscle proliferation, macrophage activation and cytokine production (Pilz S *et al.*, 2016) [7]. Vascular smooth muscle cell proliferation, the renin-angiotensin-aldosterone system and macrophage invasion of blood vessel walls are activated by vitamin D deficiency. In addition, parathyroid hormone secretion and inflammatory cytokine gene expression are increased. All these pathological processes result in decreased vascular compliance, increased vascular calcification and inflammation, which may contribute to the development of arterial stiffnesss (Nakashima A *et al.*, 2016) [3].

CONCLUSION

This study showed that there is a high prevalence of 25(OH)D deficiency in CKD patients. Deficiency of 25(OH)D is a contributing factor in the development of arterial stiffness in CKD.

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