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Co-rrelation of serum vitamin D with chronic kidney disease in an Indian population-A prospective study from central India

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Abstract
Vitamin D levels may be able to predict early kidney disease Researchers found that those who were deficient in vitamin D were more than twice as likely to develope albuminuria over a period of time. Albuminuria is an early indication of kidney damage as healthy kidneys capture protein for use in the body.There have been a number of studies establishing a relationship between vitamin D levels and kidney disease.It is unknown if vitamin D levels are a cause or condition of kidney damage. Vitamin D deficiency and insufficiency were defined as a serum 25-hydroxyvitamin D concentration < 10 ng/mL and 10–30 ng/mL, respectively.25-hydroxyvitamin D levels were significantly lower according to severity of renal impairment The prevalence of vitamin D deficiency/insufficiency was from CKD stage 3a, 3b, 4 and 5; 66.6%, 70.9%, 74.6%, and 84.7% ($p<0.001$)respectively. This study demonstrates that 25-hydroxyvitamin D insufficiency and deficiency are more common and associated with the level of kidney function in Indian population In summary, the present data indicate a high prevalence of 25-hydroxyvitamin D deficiency and insufficiency in Indian patients with moderate and severe CKD not on dialysis.25-hydroxyvitamin D deficiency is strongly and independently associated with CKD.

Keywords: co-rrelation, vitamin D, chronic kidney disease

Introduction

In the past decade, an abundance of evidence has detailed a more expanded array of actions involving numerous regulatory processes for vitamin D in the body [1, 3]. The relevance of this is underscored by the parallel realization of the epidemic of hypovitaminosis D in the general population and by the already-established disproportionately high incidence of hypovitaminosis D in patients with chronic kidney disease (CKD) [1, 4, 6]. New evidence has now established that the role of vitamin D is no longer solely restricted to its classical function of maintaining calcium and phosphate homeostasis [1, 3, 7]. Vitamin D appears to play a more extensive role as a cell differentiating and antiproliferative factor with actions in a variety of tissues [1, 3, 4], including the renal, cardiovascular, and immune systems [7, 9]. In patients with CKD, the new non-classical role of vitamin D also encompasses regulation of the renin-angiotensin system (RAS) [3, 5] and the nuclear factor (NF) κB pathway [3], two pathways involved in a broad range of pathological processes.[3] These emerging findings establish a new paradigm in approaching treatment to address both the classical and non-classical effects of vitamin D in patients affected by vitamin D deficiency, particularly those with CKD. It appears that adequate replacement of vitamin D in deficient populations could potentially reduce premature morbidity and mortality. [3, 5] These new data present convincing evidence for the necessity of administration of vitamin D both in the 25 and 1,25 forms to supplement both the classical endocrine renal 1-alpha-hydroxylase vitamin D pathway as well as the autocrine intracellular 1-alpha-hydroxylase pathway through which vitamin D has now been shown to function.[1] The implications of these new data will serve to shift the approach to vitamin D replacement in CKD patients into a new era where use of vitamin D is no longer solely for the treatment of secondary hyperparathyroidism.[1, 6] Vitamin D is a prehormone obtained through the diet or via skin synthesis. It is subsequently activated in a sequential 2-step process, involving first 25-hydroxylation in the liver to produce 25-(OH) vitamin D and then 1-hydroxylation, which until recently was thought to occur primarily in the kidney, to produce the active product 1,25 vitamin D or calcitriol [2, 4, 7]. The traditional dogma was that the 1,25 renal-activated end-product was responsible for all of the effects of the active vitamin D hormone in the body and that these effects were restricted to regulation of bone and mineral metabolism [1, 2].

A more expanded role for 25-(OH) Vitamin D was suggested by the ubiquitous existence of the vitamin D receptor in the body [5, 7, 10], the presence of at least 800 human genes for which there is a vitamin D response element [2, 7], and the wide distribution of the 1-alpha-hydroxylase in non-renal tissues such as the skin, vascular

smooth muscle cells, pancreas, kidney, heart, immune system, intestine and sarcoid tissue [2, 4]. In addition, it has been noted that the incidence of certain chronic non-osseous diseases, such as cancers and chronic infections, were strongly correlated with latitude and therefore lower cutaneous synthesis of vitamin D [2, 7]. Evidence now shows that, in addition to the classical pathway for activation of 25-(OH) vitamin D to 1,25-(OH)2vitamin D, a peripheral autocrine pathway exists and results in calcitriol synthesis in a variety of peripheral (non-renal) tissues [1, 2]. In fact, it appears that the bulk of daily metabolic utilization of 25-(OH)-vitamin D is via the peripheral autocrine pathway, although its contribution to circulating 1,25-(OH)2vitamin D is minimal due to immediate local degradation [2]. Calcitriol synthesized in this manner in the cells and tissues that possess these pathways serves as a critical component in the signaling cascades that bridge external stimuli to gene transcription.[1, 2] By binding with its intracellular vitamin D receptor (VDR) in these tissues, calcitriol can regulate cellular proliferation and differentiation, inflammation, the immune system and the endocrine system, including RAS, insulin resistance and lipid metabolism [1, 10]. The discovery of this non-classical pathway (which is also present in renal tissue) has brought new significance to the importance of addressing nutritional vitamin D deficiency given the potential role that hypovitaminosis D may play in multiple chronic diseases such as diabetes, chronic infectious processes, hypertension, cardiovascular disease and CKD [1, 5]. Vitamin D deficiency is of high prevalence in the general population [2, 5, 7] and patients with CKD are affected to an even greater degree [1, 5].

Presence of vitamin D deficiency, both in the general population and in patients with chronic kidney disease (CKD), is based mainly on the effects of vitamin D on calcium homeostasis and bone health. Bone disorders, mineral abnormalities and vascular calcification in individuals with moderate to advanced CKD seem to be related to a progressive deficiency of active vitamin D and worsening secondary hyperparathyroidism. Serum levels of 25-hydroxyvitamin D are also inversely associated with serum PTH level both in patients with CKD[1] and in those without this disease [2]. Serum 25-hydroxyvitamin D is also an inverse predictor of disease progression and death in patients with CKD [3, 4]. A high prevalence of mineral metabolite abnormalities and vitamin D insufficiency or deficiency occurs in a large number of US adults with CKD and undergoing dialysis [5, 6]. Recent observations have indicated that serum 25-hydroxyvitamin D is significantly lower in participants with a severe decrease in estimated glomerular filtration rate (GFR) compared with those with normal kidney function [7]. Therefore, the recent Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Mineral Metabolism and Disease in Chronic Kidney Disease recommend the measurements of 25-hydroxyvitamin D levels in patients with CKD not yet on dialysis. Currently, clinical evidence supporting a strong link between vitamin D insufficiency or deficiency and the risk of CKD, CVD and infectious diseases both in the general population and in patients with CKD, is rapidly accumulating [8, 9, 10, 11]. Previous reports come from small clinic-based samples and may not represent the true association between vitamin D status and kidney function in the CKD population [12, 13]. In addition, a higher serum vitamin D level is expected in inhabitants of the tropics vis-a-vis inhabitants of nontropical regions, due to greater sun exposure and increased production of vitamin D. Indian patients with CKD are more likely to have high sun exposure; however, no clinical study in the Indian CKD population has been performed to support this assertion. Therefore, we determined the relationship between hypovitaminosis D and CKD stages in this population.

Method

A cross-sectional study was carried out in 724 CKD patients who were followed up in MOPD of Dr RLM institute of Medical Sciences Lucknow between Apr, 2017 and December 31, 2019 having their 25-hydroxyvitamin D level assessed. For the purposes of the present study, we included participants with estimated GFR < 60 mL/min/1.73 and without dialysis.All biochemical analyses of blood samples were conducted at biochemistry dept of institute. An estimate of the GFR was obtained by CKD-EPI creatinine equation[14] Irrespective of the presence or absence of proteinuria, CKD was defined as a GFR of < 60 mL/min per 1.73 m^2. The CKD subjects were categorized by the KDIGO Clinical Practice Guidelines for Chronic Kidney Disease in four stages: CKD stage 3a (45–59 mL/min/1.73 m^2), CKD stage 3b (30–44 mL/min/1.73 m^2), CKD stage 4 (15–29 mL/min/1.73 m^2) and CKD stage 5 (<15 mL/min/1.73 m^2).

Serum 25-hydroxyvitamin D concentrations, as a reliable measure of overall vitamin D status, were measured by electrochemiluminescence immunoassay A 25-hydroxyvitamin D deficiency was defined as having levels less than 10 ng/mL, and insufficiency, as having levels of 10 to 30 ng/mL.

Statistical analysis

Statistical differences in variables were compared using one-way analysis of variance (ANOVA) and unpaired Student's t-test for normally distributed variables and Kruskal-Wallis Test for non-normally distributed variables. Categorical variables were recorded as frequency counts, and intergroup comparisons were analyzed by chi-square test. Associations between vitamin D status and CKD stage 5 were analyzed by multivariate logistic regression analysis [Odds ratio with 95% confidence intervals (CI)] and the multivariate analyses were conducted after including variables such as age, gender, hemoglobin, serum albumin, calcium, phosphate and alkaline phosphatase. Statistical significance was accepted if $P<0.05$. Data analysis was performed using SPSS

Result

Subjects with CKD and estimated GFR of 34.19 ± 17.39 mL/min/1.73 m^2 were screened for 25-hydroxyvitamin D levels. The participants were all Indian.52.4% were male, 38.6%, had type 2 diabetes and 64.4% had

hypertension as a comorbid disease. There were 724 subjects grouped to investigate for differences in clinical and laboratory characteristics according to CKD status. The values included age, gender, GFR, hemoglobin, serum albumin, calcium, phosphorus, alkaline phosphatase and intact-PTH differring among the CKD stages. Notably, levels of 25-hydroxyvitamin D significantly lower according to severity of renal impairment (CKD stage 3a: 27.84±14.03 ng/mL, CKD stage 3b: 25.86±11.14 ng/mL, CKD stage 4: 24.09±11.65 and CKD stage 5: 20.82±9.86 ng/mL, respectively ($p<0.001$) of the 724 CKD patients, 72.7% had a diagnosis of 25-hydroxyvitamin D insufficiency defined as vitamin D ≤ 30 ng/mLto > than 10ng/mL and 5.3% of 25-hydroxyvitamin D deficiency defined as less than 10 ng/mL. As shown in Figure 1, significant differences were observed in stratified patients with 25-hydroxyvitamin D ≤ 30 ng/mL according to the CKD stages (CKD stage 3a; 66.6%, CKD stage 3b; 70.9%, CKD stage 4; 74.6% and CKD stage 5; 84.7% respectively with $p<0.001$). An increasing prevalence of vitamin D deficiency with increasing severity of CKD was also found. Estimated GFR, serum albumin, calcium and hemoglobin occurred significantly less among patients with levels of 25-hydroxyvitamin D ≤ 30 ng/mL.(Refer Table-1)

Table 1: Characteristic of patients as per CKD category

GFR	<15ml/mt	15-29/ml/mt	30-44ml/mt	45-59ml/mt
Number	145	129	210	241
Age (yr)	63.30+-16.88	21.26+-12.70	72.60+-11.46	61.80+-12.10
Male (n-%)	72(49.20%)	65(50%)	120(57%)	123(51%)
GFR ml/mt	7.62+-3.34	22.71+-4.20	38.1+-4.22	43.53+-+-4.25
BUN (mg/dl)	49.27+-18.20	34.97+-1135	23.40+-6.75	17.95+-5.12
Hb (gm/dl)	10.82+-1>71	11.07+-1.57	12.+-1.7	12.56+-1.65
Creatinine (mg/dl)	7.34+-3.27	2.48+-0.55	1.61+-0.25	1.23+-0.19
Albumin (gm/dl)	3.99+-0.55	4.8+-0.49	4.25+-0.39	4.33+_0.42
Calcium (mg/dl)	9.3+_	9.37+_0.63	9.5+_0.64	9.56+_0.56
Phosphorus (mg/dl)	4.53+-1.43	3.66+-0.56	3.46+-0.56	3.37+-0.56
S.25 (OH) D (ng/ml)	20.82+-9.86	24.09+-11.6	25>86+_11.14	27.84+_11.29
S.Alk PO4	168.39+-329..4	91.33+50.15	71.11+-57.81	71.82+-32.15

Data or mean+-SD and Median with interquartile ranges;$p<0.01$;$p<0.05$ versus GFR 45-59ml/min/1.73m^2

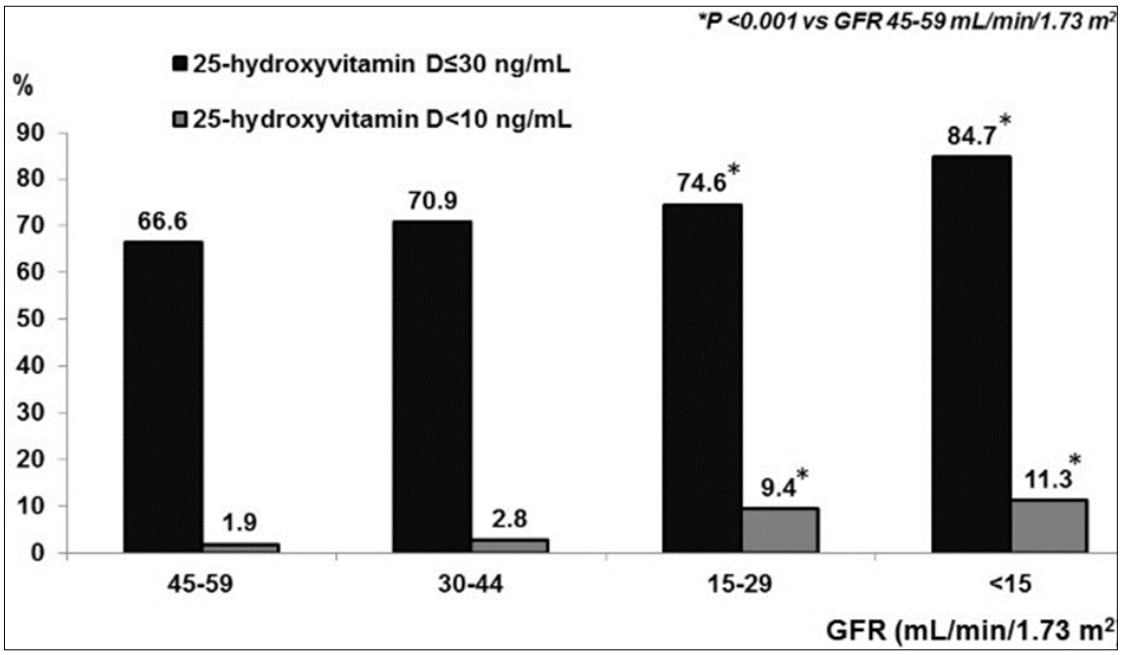

Fig 1

Table 2: Vitamin D insufficiency and deficiency with other factors 25(OH) Vitamin D(ng/ml)

Variable	>30ng/ml	<30ng/ml
Age (years	70.19+_12.37	6.34+_13.59
Male (n-%)	60(58.38)	138(50.70)
GFR (ml/ml)	30.08+_15.83	33.22+_17.99
BUN mg/dl	26.08+_13.15	30.8+_17.23
Creatinine (mg/ml)	2.22+_2.09	2.99+_3.01
Hb (gm/dl)	11.8+_1.87	11.54+_1.72

Albumin (gm/dl)	4.29+_0.48	4.14+_0.49
Calcium (mg/dl)	9.53+_0.65	9.4+_0.74
Phosphorus (mg/dl)	3.56+_0.79	3.85+_1.08
S.Alk po4 (microgram/L)	79.75+_41.88	97.41+_95.91

Data are mean+-SD and median with interquartile ranges,p-value versus 25(OH)vitamin D>30ng/dl

Table 3: Vitamin D insufficiency/deficiency associated with advanced CKD stage defined as Estimated GFR less than15ml/min/1.73m^2 in the all CKD subjects as evaluated by multiple logistic regression analysis

25(OH) vitamin	Unadjusted OR	P Value	Adjusted OR	P Value
	95%(CI)		95%(CI)	
<30ng/dL	2.15(1.56,2.97)	<0.001	2.19(1.07,4.48)	<0.032
10-30ng/ml	1.93(1.39,2.67)	<0.001	1.84(0.88,3.82)	<0.104
<10ng/ml	8.72(5.32,14.29)	<0.001	16.76(4.89<57.49)	<0.001
>30ng/ml	2.16(1.58,2.99)	0.001	2.14(1.03,4.40)	0.030

Multivariate analysis was done after including variables eg Age, gender, Hb, S. A lbumin, Calcium, Phosphate and Alkaline phosphatase P value versus S, 25(OH) vitamin D<30ng.dl

Vitamin D insufficiency/deficiency associated with advanced CKD stage

Adjusted odds ratio for advanced CKD stage in subjects categorized based on vitamin D deficiency and insufficiency. Using multivariate logistic regression analysis, an inverse association was observed between serum 25-hydroxyvitamin D ≤ 30 ng/mL and prevalent CKD stage 5 [adjusted odds ratio 2.19 (95% CI 1.07 to 4.48)] in the CKD population after adjusting for potential confounders. Additionally, the association between serum 25-hydroxyvitamin D < 10 ng/mL and prevalent CKD stage 5 [adjusted Odds ratio 16.76 (95% CI 4.89 to 57.49)] remained statistically significant in CKD participants, even after adjusting confounding factors.

Discussion

The principal finding of the present study is that vitamin D insufficiency and deficiency are widely prevalent among CKD patients, similar to the general population. Regardless of the geographic location in India, serum 25-hydroxyvitamin D level ≤30 ng/mL was present in 66.6-84.7% of patients with stage 3a-5 CKD. Also low vitamin D status has been reported among Asian populations with normal kidney function despite it being a tropical region [15, 1] This is one of few epidemiological study in Asian tropical countries to use estimated GFR calculations to demonstrate that vitamin D insufficiency and deficiency is associated with lower estimated GFR.

Our findings complement recent observations suggesting that vitamin D deficiency is strongly associated with greater stages of CKD among adult participants. Among 14,679 US adult participants in the Third National Health and Nutrition Examination Survey (NHANES III), mean serum 25-hydroxyvitamin D level was lower in patients with stage 4–5 CKD compared with those with normal kidney function (24.6 vs. 29.3 ng/mL, P <0.001)[7] Similarly, another study measured serum 25-hydroxyvitamin D levels in patients with CKD. The overall mean serum level of 25-hydroxyvitamin D was 19 ±14 ng/mL and only 29% of the 65 patients with stage 3 CKD and only 17% of 113 patients with stage 4 CKD had vitamin D insufficiency and deficiency[18] Moreover, participants with 25-hydroxyvitamin D levels <15 ng/mL had a 2.6-fold greater incidence of ESRD than those with levels ≥15 ng/mL during a long-term follow-up [19, 20, 21]. In addition, few studies demonstrated that low 25-hydroxyvitamin D levels were independently associated with albuminuria in CKD and type 1 diabetes, but they did not find evidence linking low concentrations of 25-hydroxyvitamin D to early GFR loss Thus, current data and our finding indicate that vitamin D deficiency/insufficiency is an extremely frequent condition in patients with CKD, especially those with an estimated GFR of less than 15 mL/min/1.73 m^2.

Our results demonstrate a graded relationship between serum 25-hydroxyvitamin D and the risk for kidney disease among subjects with CKD not undergoing dialysis. A causal relationship has yet to be proved by intervention trials using vitamin D. Several mechanisms might explain the 25-hydroxyvitamin D deficiency in the CKD population. First, almost patients with CKD have restricted protein and caloric intake, so vitamin D is relatively low [22]. Second, many CKD patients have limited outdoor physical activities with reduced exposure to sunlight [22]. Finally, greater loss of urinary vitamin D metabolites occurs in patients with overt proteinuria [23]

Increasing evidence supports that vitamin D metabolism affects the risk of CKD, although the underlying molecular mechanism of this association remains hidden. Mounting evidence from clinical studies has demonstrated an inverse relationship between circulating vitamin D levels and blood pressure and/or abnormalities of the renin angiotensin-aldosterone system (RAAS). The RAAS plays a key role in regulating blood pressure, vascular remodeling and progressive kidney damage [20]. In animal models, inhibiting 1,25(OH)(2)D synthesis led to an increase in renin expression, whereas injecting 1,25(OH)(2)D led to renin suppression [25]. Hence, 1,25(OH)(2)D is a novel negative endocrine regulator of the RAAS [26] Moreover, replacement with pharmacologic doses of vitamin D receptor agonists in animal models of kidney disease consistently show reduced albuminuria, abrogated glomerulosclerosis, and glomerular inflammation [28]. Recently, a cohort study found that serum 25-hydroxyvitamin D concentration was an independent inverse predictor of disease progression and death in patients with stages 2–5 CKD [3]. Collectively, these data suggest a potential renoprotective effect of vitamin D supplementation in patients with advanced CKD.

This study has several strengths including the large number of participants, the complete nature of the dataset and the ability to adjust to multiple CKD risk factors. Despite the comprehensive nature of the dataset, limitations occurred in the study. We enrolled only Thai CKD patients in Bangkok, so caution is needed in generalizing our finding with other populations. The CKD EPI formula was not tested for accuracy in Thai population and thus may be used for relative measurements of GFR and comparisons between vitamin D deficiency and non-vitamin D deficiency. Finally, our selection of subjects might have been biased. Our participants were mainly in the tertiary care center. This might be one reason why more aging and chronically ill subjects participated

The main finding of the present study is that vitamin D insufficiency and deficiency are widely prevalent among Indian CKD patients, similar to the general population. Regardless of the geographic location in India, serum 25-hydroxyvitamin D level ≤30 ng/mL was present in 66.6-84.7% of patients with stage 3a-5 CKD. Also low vitamin D status has been reported among Asian populations with normal kidney function despite it being a tropical region [15, 17] This is one of few epidemiological study in Asian tropical countries to use estimated GFR calculations to demonstrate that vitamin D insufficiency and deficiency is associated with lower estimated GFR.

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Our results demonstrate a graded relationship between serum 25-hydroxyvitamin D and the risk for kidney disease among subjects with CKD not undergoing dialysis. A causal relationship has yet to be proved by intervention trials using vitamin D. Several mechanisms might explain the 25-hydroxyvitamin D deficiency in the CKD population. First, almost patients with CKD have restricted protein and caloric intake, so vitamin D is relatively low [21, 22, 23]. Second, many CKD patients have limited outdoor physical activities with reduced exposure to sunlight [22]. Finally, greater loss of urinary vitamin D metabolites occurs in patients with overt proteinuria [23].

Increasing evidence supports that vitamin D metabolism affects the risk of CKD, although the underlying molecular mechanism of this association remains hidden. Mounting evidence from clinical studies has demonstrated an inverse relationship between circulating vitamin D levels and blood pressure and/or abnormalities of the renin angiotensin-aldosterone system (RAAS). The RAAS plays a key role in regulating blood pressure, vascular remodeling and progressive kidney damage [24, 25, 26, 27] In animal models, inhibiting 1,25(OH)(2)D synthesis led to an increase in renin expression, whereas injecting 1,25(OH)(2)D led to renin suppression [25, 27]. Hence, 1, 25 (OH)(2)D is a novel negative endocrine regulator of the RAAS [26]. Moreover, replacement with pharmacologic doses of vitamin D receptor agonists in animal models of kidney disease consistently show reduced albuminuria, abrogated glomerulosclerosis, and glomerular inflammation [27] Recently, a cohort study found that serum 25-hydroxyvitamin D concentration was an independent inverse predictor of disease progression and death in patients with stages 3–5 CKD [3]. Collectively, these data suggest a potential renoprotective effect of vitamin D supplementation in patients with advanced CKD.

Conclusion

In summary, the present data indicate a high prevalence of 25-hydroxyvitamin D deficiency and insufficiency in Indian patients with moderate and severe CKD not on dialysis.25-hydroxyvitamin D deficiency is strongly and independently associated with CKD.

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Conflict of interest
None

Ethical Clearance
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