The prevalence of vitamin D deficiency in pre-dialysis patients with chronic kidney disease

Występowanie niedoboru witaminy D u jeszcze niedializowanych chorych na przewlekłą chorobę nerek

Hari Krishan Aggarwal, Deepak Jain, Anshul Mittal, Sunil Pawar, Rajpal Verma

Department of Medicine, Pt B D Sharma University of Health Sciences Rohtak, Rohtak, India
Head of the Department: Hari Krishan Aggarwal MD

Studia Medyczne 2015; 31 (2): 75–81
DOI: 10.5114/ms.2015.52904

Key words: proteinuria, chronic kidney disease, intact parathyroid hormone (iPTH), 25 hydroxy vitamin D, 1,25 dihydroxy vitamin D.
Słowa kluczowe: proteinuria/białkomocz, przewlekła choroba nerek, nietknięta (kompletna) forma parathormonu (iPTH), 25-hydroksywitamina D, 1,25-dihydroksywitamina D.

Abstract

Introduction: Reduced vitamin D levels were seen early in the course of chronic kidney disease (CKD). Its prevalence increased and severity worsened with the progression of CKD.
Aim: To assess the prevalence of vitamin D deficiency in pre-dialysis CKD patients.
Material and methods: In the study 100 adult patients were divided into three groups depending on estimated glomerular filtration rate (eGFR). Group A consisted of 30 patients with eGFR between 30–49 ml/min, group B consisted of 33 patients with eGFR between 15–29 ml/min, and group C had 37 patients with eGFR less than 15 ml/min. Renal functions, intact parathyroid hormone, 25 hydroxy vitamin D, and 1,25 dihydroxy vitamin D were measured at baseline.
Results: The mean serum phosphate and iPTH levels increased steadily as CKD progressed. On the other hand, mean corrected serum calcium levels, 25 hydroxy vitamin D, and 1,25 dihydroxy vitamin D decreased progressively in group A, B, and C. There was a significant increase in mean serum iPTH level from group A to group C ($p < 0.05$). The mean level of 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D showed a trend of declination from group A to C ($p < 0.05$). Both 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D positively correlated with eGFR. There was negative correlation of 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D with iPTH and proteinuria.
Conclusions: The study concluded that both prevalence and severity of low 25 hydroxy and 1,25 dihydroxy vitamin D increases with progression of CKD. Their levels were negatively correlated to factors like parathyroid hormone levels and proteinuria.

Streszczenie

Wprowadzenie: W przebiegu przewlekłej choroby nerek już we wczesnym etapie obserwuje się zmniejszone stężenie witaminy D, co ma wpływ na jej postęp i ciężki charakter.
Cel pracy: Ocena występowania niedoboru witaminy D u jeszcze niedializowanych chorych na przewlekłą chorobę nerek.
Materiał i metody: W badaniu wzięło udział 100 dorosłych chorych, których podzielono na trzy grupy w zależności od poziomu szacunkowego współczynnika filtracji kłębuszkowej (eGFR). Grupa A obejmowała 30 pacjentów, u których eGFR wynosił 30–49 ml/min, grupa B – 33 pacjentów, u których eGFR wynosił 15–29 ml/min, a grupa C – 37 pacjentów, u których eGFR wynosił poniżej 15 ml/min. Na początku badania dokonano oceny funkcji nerek, oznaczono stężenie nietkniętej (kompletnej) formy parathormonu (iPTH) oraz witaminy D w dwóch postaciach – 25(OH)D i $1,25(OH)_2D$.
Wyniki: Średnie stężenie w surowicy fosforanu i iPTH zwiększało się w miarę postępu przewlekłej choroby nerek. Średnie stężenie w surowicy wapnia, 25(OH)D i $1,25(OH)_2D$ stopniowo zmniejszało się w grupach A, B i C. Zaobserwowano istotny wzrost średniego stężenia w surowicy iPTH od grupy A do grupy C ($p < 0,05$), a także tendencję spadkową średniego stężenia 25(OH)D i $1,25(OH)_2D$ w grupach od A do C ($p < 0,05$). Stwierdzono pozytywną zależność 25(OH)D i $1,25(OH)_2D$ od współczynnika eGFR, a także negatywną zależność 25(OH)D i $1,25(OH)_2D$ od iPTH i białkomoczu.
Wnioski: Wraz z postępem przewlekłej choroby nerek zwiększa się występowanie niedoboru oraz bardzo niskich stężeń 25(OH)D i $1,25(OH)_2D$. Stężenie obu postaci witaminy D wykazywało negatywną zależność od takich czynników, jak stężenie parathormonu i białkomocz.

Introduction

Chronic kidney disease (CKD) is a major public health problem in developed and developing countries alike, leading to decreased quality of life across the globe. It is a well-known fact that patients of CKD are at increased risk for mortality as well as morbidity due to the myriad complications associated with this disease entity. Bone disorders, mineral abnormalities, and vascular calcification in individuals with moderate to advanced CKD secondary to a progressive deficiency of active vitamin D and worsening secondary hyperparathyroidism contribute largely to the morbidity and mortality in patients with renal failure [1].

Vitamin D is synthesised in the skin or ingested in the diet and is transported to the liver, where it is hydroxylated in the 25 position to yield 25 hydroxy vitamin D, which is the major circulating and storage form of vitamin D and hence is considered as the most reliable index of vitamin D level in the body. 25 hydroxy vitamin D is further hydroxylated by the enzyme 1α hydroxylase in the kidney to yield 1,25-dihydroxy vitamin D, which is the major endocrine and active form of vitamin D. This metabolite is responsible for the effects of vitamin D on calcium and phosphorus metabolism, bone health, and the regulation of parathyroid gland function [2, 3]. All patients with CKD are considered to have deficiency of 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D deficiency when levels fall below 20 ng/ml and 22 pg/ml, respectively [4]. Although decrease in renal 1α hydroxylase activity due to decreased renal mass and reduced availability of substrate 25 hydroxy vitamin D appears to be the principal reason behind the decreased levels of 1,25 dihydroxy vitamin D, there are other causes like hyperuricaemia, uraemia, and metabolic acidosis, which further depresses 1α hydroxylase activity [5]. Recently discovered fibroblast growth factor (FGF23) inhibits 1α hydroxylase activity and decreases the synthesis of 1,25 dihydroxy vitamin D, which plays an important role in the metabolism of vitamin D especially in patients of CKD [6].

Several studies have documented that early decline in glomerular filtration rate (GFR) leads to a decrease in vitamin D levels and hyperparathyroidism, even before there are changes in calcium and phosphorus metabolism. In most patients levels of 1,25 dihydroxy vitamin D start declining to a lower limit of normal in stage 2 of CKD, and by the time patients progress from stage 3 to stage 5 most of them have low levels of 1,25 dihydroxy vitamin D. Recent studies of 25 hydroxy vitamin D deficiencies in end stage renal disease (ESRD) have demonstrated that 86% of predialysis patients have a deficiency when defined by levels less than 20 ng/ml [7].

The effect of vitamin D deficiency on inflammation and on the cardiovascular system plays an important role in mortality and morbidity in CKD patients. The prolonged deficiency of 1,25 dihydroxy vitamin D together with parathyroid abnormality leads to renal osteodystrophy (ROD) and chronic kidney disease-mineral bone disorder (CKD-MBD), which can be manifested by any one or combination of the following: (1) abnormalities of calcium, phosphorous, PTH, and vitamin D metabolism, leading to increase in secondary hyperparathyroidism. (2) Bone disease. (3) Vascular or soft tissue calcification [8, 9].

Vitamin D deficiency in CKD has been studied since this condition was first described in ESRD patients. Despite its significant contribution to morbidity in CKD patients, clinicians in India tend to repetitively ignore this entity and the discomfort that its complications cause to the patients, focussing more their treatment protocol towards managing other more severe and life threatening complications of CKD. No significant contribution has been made in the prevalence or management of vitamin D deficiency in Indian literature. Our hospital, a tertiary centre catering to the needs of the entire state of Haryana, provides a significant platform to study the prevalence of vitamin D deficiency.

Aim

We planned this study to assess the spectrum, prevalence, and factors leading to vitamin D deficiency in patients of CKD, and correlated it with severity of renal dysfunction

Material and methods

This study was conducted on 100 adult pre-dialysis patients of CKD stage III-V as per NKF-DOQI classification, on regular follow-up of kidney and dialysis at the clinic at Pt. B.D. Sharma PGIMS, Rohtak, with ages ranging between 18 and 75 years. Pre-informed, written consent for enrolment in the study was obtained. The study was duly approved by the Ethical Committee of Pt. B. D. Sharma University of Health Sciences, Rohtak. Patients on dialysis and those receiving medication known to influence vitamin D, such as vitamin D-containing drugs, corticosteroids, other immune suppressive agents, hormone replacement therapy, anticoagulants, lithium, phosphate binders, and anticonvulsants, were excluded. Patients with prior parathyroidectomy were also excluded. Patients with any condition that precluded them from remaining in the study, such as alcohol, drug abuse, malignancy, psychiatric illness, and pregnancy, were also excluded. Each patient was subjected to detailed general physical examination, and the following relevant renal and other biochemical investigations were carried out.

Routine renal and other biochemical investigations including blood urea (mg/dl), serum creatinine (mg/dl), serum corrected calcium levels (mg/dl), serum phosphorous levels (mg/dl), calcium phosphate

product, serum protein (g/dl), intact parathyroid hormone (iPTH) levels (pg/ml), serum sodium (meq/l), serum potassium (meq/l), blood sugar, 24-hour urine proteinuria, 25 hydroxy vitamin D, and 1,25 dihydroxy vitamin D were carried out as per the standard methods used in the Department of Biochemistry, PGIMS, Rohtak. Estimated GFR was calculated using the four-variable MDRD equation. The patients were divided into three groups A, B, and C on the basis of severity of kidney disease. Each group consists of age- and sex-matched patients from CKD stage III, IV, and V, respectively. Group A consisted of 30 patients with eGFR between 30–49 ml/min (stage III), group B consisted of 33 patients with eGFR between 15–29 ml/min, and group C had 37 patients with eGFR less than 15 ml/min. Intact PTH was measured by chemiluminescent immunoassay (CLIA) method. 25 hydroxy vitamin D levels were measured using enzyme linked immunosorbent assay (ELISA). The patients with levels of 25 hydroxy vitamin D less than 20 ng/ml were considered deficient. 1,25 dihydroxy vitamin D was measured using radioimmunoassay (RIA). Deficiency of 1,25 dihydroxy vitamin D was defined as levels less than 22 pg/ml [4]. Corrected serum calcium was calculated using the equation 0.8 × (4-serum albumin) + observed calcium.

Statistical analysis

At the end of the study, the data was expressed as mean ± 1 SD or range. Probability values of < 0.05 were considered to be significant in all the analysis. The statistical analyses were performed using Kruskal-Wallis one way analysis of variance (ANOVA), χ^2 test, and unpaired *t* test. The correlations were tested using Spearman's Rank order correlation analysis. All statistical calculations were carried out using SPSS 20.0 software.

Results

Of a total of 100 patients, 59 were male and 41 were female. The most common cause of CKD was diabetes mellitus (30%) followed by hypertension (26%) and chronic glomerulonephritis (20%). Less frequent aetiologies included adult polycystic kidney disease, obstructive uropathy, and renal amyloidosis. The mean serum phosphate increased steadily as CKD progressed, with statistical difference among three groups. On the other hand, mean corrected serum calcium decreased progressively in group A, B, and C. The mean serum iPTH levels increased as the stage of CKD progressed. The mean serum iPTH values in group A, B, and C were 156.36 ±106.50, 262.93 ±114.80 and 350.16 ±117.51 pg/ml, respectively, and there was a statistically significant increase in mean iPTH level from group A to group C ($p < 0.05$). The mean level of 25 hydroxy vitamin D showed a trend of declination from group A to C (Table 1). The mean 25 hydroxy vitamin D level in group A was 28.14 ±12.82 ng/ml, 27.97 ±16.57 ng/ml in group B, and 19.64 ±11.88 ng/ml in group C. Comparison of levels of 25 hydroxy vitamin D between group A vs. C and B vs. C showed that the decline in levels was statistically significant ($p < 0.01$). Although the decline in levels of 25 hydroxy vitamin D between group A vs. B was not statistically significant, the mean value of 25 hydroxy vitamin D decreased between the two groups (Table 2). The mean level of 1,25 dihydroxy vitamin D also showed a trend of declination from group A to C. The

Table 1. Baseline biochemical characteristics of patients in each group

Parameter	Group A (*n* = 30)	Group B (*n* = 33)	Group C (*n* = 37)	Value of *p*
Haemoglobin [g/dl]	9.07 ±1.49	8.806 ±1.29	8.05 ±1.22	> 0.05
Blood urea [mg/dl]	85.86 ±19.62	122 ±35.95	194.10 ±51.00	< 0.01
Serum creatinine [mg/dl]	1.9 ±0.64	3.07 ±0.55	6.96 ±1.58	< 0.01
eGFR [ml/min]	38.28 ±8.14	21.86 ±4.33	7.922 ±2.47	< 0.01
Serum calcium [mg/dl]	8.26 ±0.44	7.97 ±0.44	7.52 ±0.70	< 0.01
Serum phosphate [mg/dl]	4.47 ±1.45	5.72 ±1.22	6.82 ±1.22	< 0.01

Table 2. Comparison of levels of 25 hydroxy vitamin D across three groups

25 Hydroxy vitamin D [ng/ml]	Group A (*n* = 30)	Group B (*n* = 33)	Group C (*n* = 37)
Mean ± SD	28.45 ±12.82	27.97 ±16.57	19.64 ±11.88
Groups		Value of *p*	
A vs. B		> 0.05	
A vs. C		< 0.01	
B vs. C		< 0.01	

Table 3. Comparison of levels of intact parathyroid hormone and 1,25 hydroxy vitamin D across three groups

Parameter	Group A (n = 30) Mean ± SD	Group B (n = 33) Mean ± SD	Group C (n = 37) Mean ± SD	Value of p
Serum PTH [pg/ml]	156.36 ±106.50	262.93 ±114.80	350.16 ±117.51	< 0.01
1,25 dihydroxy vitamin D [pg/ml]	20.39 ±8.84	11.03 ±5.505	10.38 ±6.22	< 0.01

mean 1,25 dihydroxy vitamin D levels were 20.39 ±8.84 pg/ml in group A, 11.03 ±5.50 pg/ml in group B, and 10.38 ±6.22 pg/ml in group C. The decline in levels of 1,25 dihydroxy vitamin D were statistically significant across the three groups ($p < 0.01$) (Table 3).

The prevalence of both 25 hydroxy vitamin D as well as 1,25 dihydroxy vitamin D increased with advancement of renal disease. The total number of patients with deficient 25 hydroxy vitamin D levels (< 20 ng/ml) increased from 8 in group A to 18 in group B and 21 in group C. The prevalence of deficiency of 25 hydroxy vitamin D was 27% in group A, 54% in group B, and 57% in group C. When we compared the above three groups by using χ^2 analysis, the results were found to be statistically significant ($p < 0.01$). The total number of patients with deficient 1,25 dihydroxy vitamin D levels (< 22 ng/ml) increased from 18 in group A to 30 in group B and 35 in group C. The prevalence of deficiency of 1,25 dihydroxy vitamin D was 60% in group A, 90% in group B, and 95% in group C. On comparison, using χ^2 analysis, the results were found to be statistically significant ($p < 0.01$) (Figure 1).

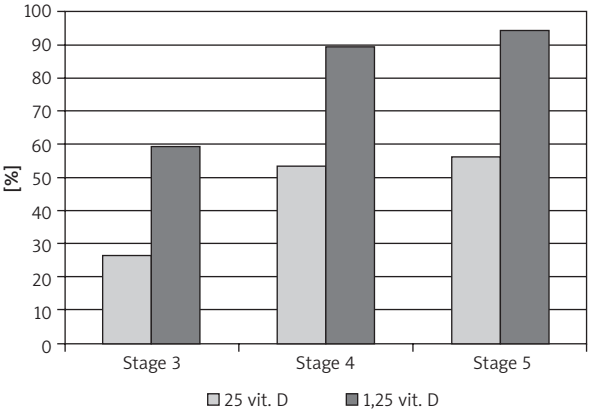

Figure 1. Prevalence of low vitamin D across study groups ($p < 0.01$)

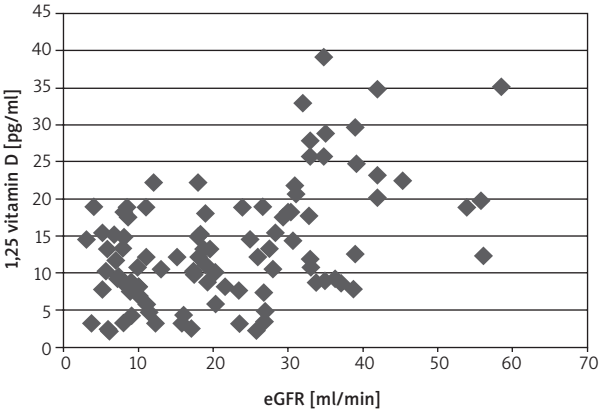

Figure 2. Correlation between 1,25 dihydroxy vitamin D and eGFR (Spearman $r = 0.482$; $p \leq 0.05$)

In correlation analysis there was statistically significant association between eGFR, corrected serum calcium, iPTH, and serum phosphate level. The corrected serum calcium was positively correlated with the eGFR while iPTH and phosphate were negatively correlated.

Both 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D were positively correlated with eGFR (Figure 2). On further analysis, when the association of iPTH and proteinuria with 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D was studied, statistically significant negative correlation was observed (Figure 3).

Discussion

Vitamin D deficiency is considered to be a systemic disorder that is associated with abnormal regulation of calcium, phosphorous, and PTH. This leads to abnormalities in bone metabolism and increased risk of cardiovascular disease, which are an important cause of morbidity and mortality in CKD patients. Because the early initiation of appropriate therapy in CKD patients may ameliorate vitamin D abnormalities and complications associated with it, early detection and understanding the pathophysiological process underlying this abnormality is important.

Vitamin D is a major steroid hormone that is important for regulation of bone and mineral metabolism. Vitamin D controls intestinal absorption of dietary calcium, tubular absorption of calcium by the kidneys, and in conjugation with PTH mobilises calcium from the skeleton. Vitamin D is either synthesised in the skin or ingested in the diet and is transported to the liver, where it is hydroxylated at position 25 to yield 25 hydroxy vitamin D (calcidiol), which is the major storage form of vitamin D. It is further hydroxylated by 1α hydroxylase in the kidney to its most active form 1,25 dihydroxy vitamin D (calcitriol) [10].

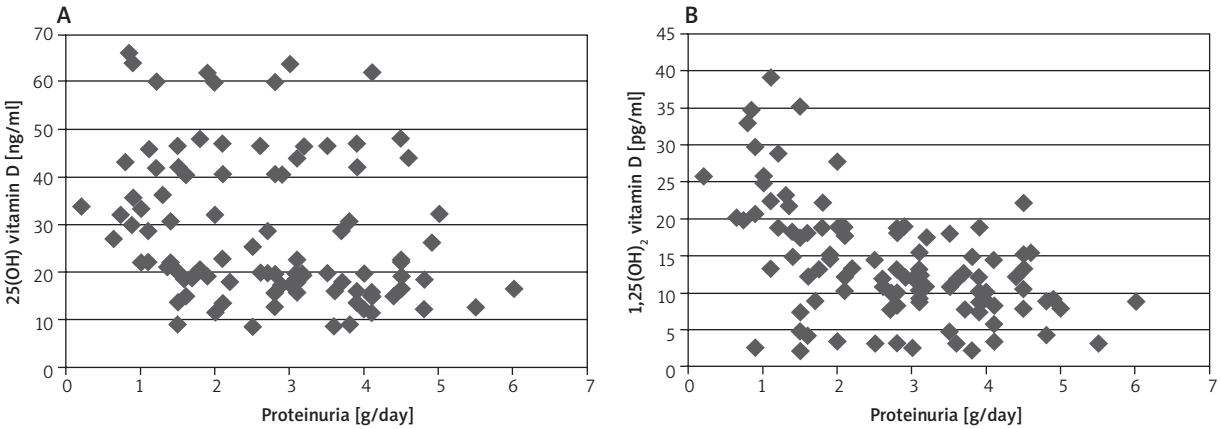

Figure 3. **A** – Correlation between proteinuria and 25 hydroxy vitamin D (Spearman $r = -0.289$; $p < 0.01$). **B** – Correlation between proteinuria and 1,25 dihydroxy vitamin D (Spearman $r = -0.522$; $p < 0.01$)

Chronic kidney disease is a state of vitamin D deficiency. The disruption of the delicate balance between vitamin D and PTH leads to increased risk of bone disease and cardiovascular complications. Though the role of vitamin D deficiency in causing bone and mineral abnormalities, vascular calcification, and secondary hyperparathyroidism is known, little is known about its prevalence and profile in the Indian population with CKD.

Bearing in mind these facts this study was planned to evaluate the vitamin D status in 100 predialysis CKD patients: 30, 33, and 37 each from CKD stage III, IV, and V, respectively, were divided into three groups A, B, C, respectively. The three groups were similar in baseline characteristics, including age, sex, ethnicity, geographical area, religion, economic status, and education level.

The present study demonstrated that mean 25 hydroxy vitamin D levels decreased significantly as the CKD progressed from stage III to stage V. Although the mean levels of 25 hydroxy vitamin D decreased across group A–C, the decline was not statistically significant. Nonetheless, on subgroup analysis the decline in 25 hydroxy vitamin D when compared between group A vs. C and B vs. C was found to be statistically significant ($p < 0.01$). The active metabolite 1,25 dihydroxy vitamin D showed a similar pattern with its levels decreasing as CKD progressed from stage III to stage V. There was a statistically significant decline in 1,25 dihydroxy vitamin D levels between the three groups ($p < 0.01$). These findings indicate that deficiency of both 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D, although beginning early in CKD, is related to the severity of kidney function, and majority of patients with advanced CKD have reduced levels with subsequent increased risk of cardiovascular disease and CKD-MBD. The study also showed that in group A and group B, which included patients of CKD stage 3 and 4 CKD, respectively, even though mean values of 25 hydroxy vitamin D were in sufficient range the mean values of 1,25 hydroxy vitamin D were in deficient range, and these decreased further as the stage of CKD progressed, highlighting the fact that decreased conversion of 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D commences as early as stage 3 of CKD. The mean serum iPTH values in group A, B, and C were 156.36 ±106.50 pg/ml, 262.93 ±114.80 pg/ml, and 350.16 ±117.51 pg/ml, respectively. The mean serum PTH levels increased from group A to group C, and the rise between three groups was statistically significant ($p < 0.01$).

Kidney is the principle site for enzyme 1α hydroxylase, which converts 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D and thus maintains its levels. There seem to be three important mechanisms for decreased activity of this enzyme in CKD: decreased renal mass, which reduces the enzyme; decreased availability of substrate 25 hydroxy vitamin D, which is due to its decreased uptake in the proximal tubular cells by receptor megalin-mediated endocytosis; and increased level of FGF 23, which inhibits the enzyme 1α hydroxylase. The activity of 1α hydroxylase is also suppressed by a constellation of problems like hyperuricaemia and metabolic acidosis and uraemia commonly seen in advanced CKD [11–13].

Most of the studies done previously have been in concordance with reduced vitamin D levels in CKD patients. Stavroulopoulos *et al.* conducted a study in 112 predialysis patients. The mean 25 hydroxy vitamin D levels for all of the participants were 21.2 ng/ml, with 80% of patients having vitamin D levels below 20 ng/ml. They concluded that 25 hydroxy vitamin D levels were positively correlated with the GFR and advancement of renal failure [14]. In another study by – Zendher *et al.* the association between CKD 3 and 5 and alteration in 25 hydroxy and 1,25 dihydroxy vitamin D concentration in 249 CKD patients was assessed, and it was concluded that levels of 1,25 di-

hydroxy were found to be low even among patients of stage 3 when compared with low 25 dihydroxy levels, and these decreased further with advancing stage of CKD [15].

We observed that prevalence both 25 hydroxy vitamin D as well as 1,25 dihydroxy vitamin D levels increased with the progression of CKD. As severity ofCKD increased, the total number of patients with 25 hydroxy vitamin D deficiency (levels < 20 ng/ml) increased from 8 in stage III to 21 in stage V. The prevalence of 25 hydroxy vitamin D deficiency increased from 27% in group A to 54% in group B and 57% in group C. With increasing severity of CKD the total number of patients with 1,25 hydroxy vitamin D deficiency (levels < 22 pg/ml) increased from 18 in stage III to 35 in stage V. The prevalence of 1,25 hydroxy vitamin D deficiency increased from 60% in group A to 95% in group C. These findings suggest that the search for vitamin D deficient patients should be commenced early in CKD so that timely therapeutic intervention when initiated can reduce associated morbidity and mortality. The findings of our study corroborated with previous studies. Satiarapoj *et al.* examined the relationship between vitamin D status and the staging of CKD in 2895 CKD patients [16]. Serum levels of 25-hydroxy vitamin D were analysed according to CKD stages, and vitamin D deficiency was defined as serum 25-hydroxy vitamin D concentrations less than 20 ng/ml. The prevalence of 25 hydroxy vitamin D deficiency in CKD stage 3a, 3b, and 4 to 5 was 66.6%, 70.9%, 74.6%, and 84.7%, respectively ($p < 0.001$). The study demonstrated that 25 hydroxy vitamin D insufficiency and deficiency are more common and associated with the level of kidney function [16]. In another study, which was done on 1814 patients of CKD, low levels of 1,25 dihydroxy vitamin D were evident at all eGFR rates: 13% in those with eGFR greater than 80 ml/min, which increased to > 60% in those with eGFR less than 30 ml/min [17].

We performed a correlation analysis to assess the relationship between eGFR, 25 hydroxy vitamin D, and 1,25 dihydroxy vitamin D. The association between loss of renal function measured by eGFR and 25 hydroxy vitamin D levels was assessed by using Spearman's Rank Order correlation test. There was a strong positive correlation which was statistically significant ($p < 0.05$). Similarly, a positive correlation was observed between eGFR and 1,25 dihydroxy vitamin D levels ($p < 0.05$).

In order to determine the factors contributing to the reduced 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D levels we performed a correlation analysis. The 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D levels were negatively correlated with iPTH, which was statistically significant ($p < 0.01$). The results were in concordance with those seen by Pitts *et al.*, who showed that in patients with moderate renal failure (GFR, 20–40 ml/min) the mean ionised calcium level was normal, plasma PTH levels and fractional excretion of phosphate (FEP) were elevated with decrement in 1,25 dihydroxy vitamin D [5]. The results were also in agreement with the study done by Jabbar *et al.*, who observed that vitamin D deficiency in 80%, and insufficiency in 13% of patients with CKD iPTH >300 pg/ml ($p = 0.04$) [18]. Secondary hyperparathyroidism in patients with chronic renal failure results from hypocalcaemia, phosphate retention, and deficiency of 1,25-dihydroxy vitamin D. Vitamin D binds to its vitamin D receptor (VDR) on the parathyroid gland and suppresses its production. It is the low circulating vitamin D levels in CKD that contribute to low VDR expression in uremic parathyroid gland, which causes increased levels of PTH both due to increased parathyroid cell number and increased PTH synthesis [19, 20].

In another correlation analysis a negative correlation of 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D levels were seen with the amount of proteinuria per day. These results were similar to these seen by Isakova, who undertook a study to assess the association between albuminuria and alteration in 25 hydroxy and 1,25 dihydroxy vitamin D concentration in 1847 CKD patients. The study concluded that albuminuria is independently associated with low 25 hydroxy vitamin D and 1,25 dihydroxy vitamin D [21].

Although seen in many previous studies, the present study showed no correlation between factors like age, sex, presence of diabetes, or hypertension and low levels of 25 hydroxy and 1,25 dihydroxy vitamin D.

Conclusions

Vitamin D deficiency leads to complications like SHPT, CKD-MBD, increased risk of vascular calcification, and CVD in CKD, especially in its advanced stage (ESRD). As most of these complications are preventable, early detection and adequate treatment of this entity must be a priority among physicians and nephrologists alike, who deal with patients of CKD on a day-to-day basis. The management of vitamin D deficiency in CKD patients differs from the general population as the disease is complicated by factors like anaemia, acidosis, hyperuricaemia, increased level of FGF 23, SHPT, and proteinuria, which affect vitamin D levels. Hence, it is imperative that every treating physician has in-depth knowledge regarding this disease process.

The present study concluded that vitamin D deficiency is seen early in the course of CKD, as estimated by levels of 25 hydroxy and 1,25 dihydroxy vitamin D. Its prevalence increases and severity worsens with the progression of CKD. The levels of vitamin D were negatively correlated to factors like parathyroid hormone levels and proteinuria. In early stages of CKD, like stages 3 and 4, even when 25 hydroxy vitamin D

was replete, the biological active form 1,25 dihydroxy vitamin D started to decline.

In developing countries like India, where monetary constraints are common, useful information on vitamin D status can be obtained by using simple, outpatient-based, non-invasive methods, such as CLIA and RIA, in predialysis patients of CKD, giving a vital opportunity to act and intervene, so that associated complications like CKD-MBD and CVD can be reduced.

Conflict of interest

The authors declare no conflict of interest.

References

1. Block GA, Cunningham J. Morbidity and mortality associated with abnormalities in bone and mineral metabolism in CKD. In: Clinical guide to the basics of bone and mineral metabolism in CKD. Chapter 4. Olgaard K (ed). National Kidney Foundation, New York 2006; 77-92.
2. St-Arnaud, Arabian A, Travers R, et al. Deficient mineralization of intramemranous bone in vitamin D-24- hydroxylase-ablated mice is due to elevated l1,25 dihydroxy vitamin D and not to the absence of 24,25 dihydroxy vitamin D. Endocrinology 2000; 141: 2658-66.
3. Jones G, Strugnell SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. Physiol Rev 1998; 78: 1193-23.
4. Jacob AI, Sallaman A, Santiz Z, Hollis BW. Defective photoproduction of cholecalciferol in normal and uremic humans. J Nutr 1984; 114: 1313-9.
5. Pitts TO, Piraino BH, Mitro R, et al. Hyperparathyroidism and 1,25 dihydroxyvitamin D deficiency in mild, moderate and severe renal failure. J Clin Endocrinol Metabol 1988; 67: 876-81.
6. Ibrahim S, Rashed L. Serum fibroblast growth factor-23 levels in chronic hemodialysis patients. Int Urol Nephrol 2009; 41: 163-9.
7. Gonzalez EA, Sachdev A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single centre observational study. Am J Nephrol 2004; 24: 503-10.
8. Martin KJ, Gonazalez EA. Metabolic bone disease in chronic kidney disease. J Am Soc Nephrol 2007; 18: 875-85.
9. Coen G, Ballanti P, Bonucci E, et al. Renal osteodystrophy in predialysis and hemodialysis patients: comparison of histologic patterns and diagnostic predictivity of intact PTH. Nephron 2002; 91: 103-11.
10. Bringhurst FR, Demay MB, Krane SM, et al. Harrison's principles of internal medicine. Vol 2 18th edn., McGraw Hill, New York 2008; 3092-95.
11. Willnow TE, Nykjaer A. Pathways for kidney-specific uptake of the steroid hormone 25-hydroxyvitamin D3. Curr Opin Lipidol 2002; 13: 255-60.
12. Farrow EG, Davis SI, Summers LJ, White KE. Initial FGF23-mediated signalling occurs in the distal convoluted tubule. J Am Soc Nephrol 2009; 20: 955-60.
13. Gattineni J, Bates C, Twombley K, et al. FGF23 decreases renal NaPi-2a and NaPi-2c expression and induces hypophosphatemia in vivo predominantly via FGF receptor 1. Am J Physiol Renal Physiol 2009; 297: F282-91.
14. Stavroulopoulos A, Porter CJ, Roe SD, et al. Relationship between vitamin D status, parathyroid hormone levels and bone mineral density in patients with chronic kidney disease stages 3 and 4. Nephrology 2008; 13: 63-7.
15. Zendher D, Landray MJ, Wheeler DC, et al. Cross sectional analysis of abnormality of mineral homeostasis, vitamin D and parathyroid hormone in cohort of predialysis patients. Nephron Clin Pract 2007; 103: 109-16.
16. Satirapoj B, Limwannata P, Chaiprasert A, et al. Vitamin D insufficiency and deficiency with stages of chronic kidney disease in an Asian population. BMC Nephrol 2013; 14: 206.
17. Levin A, Bakris G, Motich M, Smulders M. Prevalence of abnormal vitamin D calcium PTH and phosphorus in patients with CKD: results of the study to evaluate early kidney disease. Kidney Int 2007; 71: 31-8.
18. Jabbar Z, Aggarwal PK, Chandel N, et al. Noninvasive assessment of bone health in Indian patients with chronic kidney disease. Indian J Nephrol 2013; 23: 161-7.
19. Kawahra M, Iwassaki Y, Sakaguchi K, et al. Predominant role of 25(OH) in the negative regulation of PTH expression: clinical relevance of hypovitaminosis D. Life Sci 2008; 82: 677-83.
20. Healy KD, Vanhooke JL, Prahl JM, Deluca HF. Parathyroid hormone decreases renal vitamin D receptor expression in vivo. Proc Natl Acad Sci USA 2005; 102: 4724-8.
21. Isakova T. Vitamin D deficiency inflammation and albuminuria in CKD: complex interaction. J Ren Nutr 2011; 21: 295-302.

Address for correspondence:

Deepak Jain MD
Department of Medicine
Pt B D Sharma University of Health Sciences Rohtak
124001 Rohtak, India
Fax: +91 9416147887
E-mail: jaindeepakdr@gmail.com