Vitamin D in Chronic Kidney Disease

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ABSTRACT

Vitamin D deficiency is widespread in both the pediatric and adult chronic kidney disease (CKD) population. CKD is characterized by dysregulation of vitamin D and mineral metabolism. Secondary hyperparathyroidism and its management puts patients with CKD at increased cardiovascular risk. Emergence of experimental and some clinical data suggesting beneficial effects of vitamin D on proteinuria, blood pressure, inflammation and cardiovascular outcomes has pushed it to the center stage of CKD research. Pediatric data on vitamin D dysregulation and its consequences are still in its infancy. Ongoing prospective studies such as Chronic Kidney disease in Children (CKiD) and the Cardiovascular Comorbidity in Children with CKD (4 C) should help to delineate the evolution of disturbances in mineral metabolism and its adverse effects on growth, CKD progression and cardiovascular outcomes.

KEYWORDS: Hyperparathyroidism, Cardiovascular, Proteinuria, Hypertension, Inflammation

INTRODUCTION
In the past decade vitamin D has become the subject of intense scientific inquiry and has found a new place under the sun. Secondary to the discovery of 1-α hydroxylase enzyme and vitamin D receptor (VDR) in non-renal tissues there have been numerous preclinical studies centered on the non-classical actions of vitamin D.

These novel actions of vitamin D are of great importance to nephrologists and have generated tremendous interest in clinical research aimed at discerning its role in chronic kidney disease.

Vitamin D Physiology
Vitamin D is either synthesized endogenously in the skin after sunlight exposure or ingested in the diet. 7-dehydrocholesterol is converted to previtamin D3 by solar UVB radiation which is converted to vitamin D3. Vitamin D2 (from food sources such as dairy products, fortified breads and cereals, oily fish and supplements) and D3 are transported to the liver, where they are hydroxylated in the 25 position to yield 25-hydroxyvitamin D [25(OH)D], which is the main storage form of vitamin D. It has a half-life of 2–3 wk and is measured to assess vitamin D status. 25 (OH)D is further hydroxylated by the enzyme 1-α-hydroxylase in the kidney proximal tubule, to yield 1, 25-dihyroxyvitamin D [$1,25(OH)_2D$], which is the active form of vitamin D, and is responsible for its biologic actions [1]. The half-life of $1,25(OH)_2D$ is 8–10 h and its levels are affected by changes in calcium, phosphorus, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF 23) levels. For these reasons $1,25(OH)_2D$ levels are not a good reflection of vitamin D status. Both 25(OH)D and $1,25(OH)_2D$ are converted to biologically inactive metabolites by 25 hydroxyvitamin D-24-hydroxylase. This enzyme is activated by $1,25(OH)_2D$ and FGF-23 and helps regulate levels of 25 (OH)D and $1,25(OH)_2D$.

Vitamin D Actions

Calcemic Actions
The well-known action of vitamin D is to maintain serum calcium and phosphorus levels. $1,25(OH)_2D$ enhances intestinal calcium absorption in the small intestine by increasing the expression of calcium transport proteins, epithelial calcium channel TRPV6 and Calbindin 9 K [2]. Without vitamin D, only 10–15 % of dietary calcium and about 60 % of phosphorus are absorbed. In the presence of $1,25 (OH)_2D$, the efficiency of intestinal calcium and phosphorus absorption increases to 30–40 % and 80 %, respectively [3].

$1,25(OH)_2D$ is a potent negative regulator of PTH production. It binds with the vitamin D receptor (VDR) complex on parathyroid cells and down regulates PTH gene expression, increases expression of VDRs and increases transcription of the calcium sensing receptors (CaSR) [4]. A recent study has shown that the parathyroid glands may function as a vitamin D autocrine system as they express 1-α hydroxylase and also 25-hydroxylase, allowing the gland to produce their own $1,25(OH)_2D$ to regulate PTH production [5]. This may explain why PTH levels correlate inversely with 25(OH)D levels in mild to moderate CKD with no changes in $1,25(OH)_2D$ levels [6]. A prolonged deficiency of vitamin D metabolites leads to a need for higher serum calcium levels and vitamin D doses as there is a markedly reduced VDR and CaSR expression by the parathyroid cells [4].

In bones, $1,25(OH)_2D$ induces pre-osteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone to maintain their respective

levels in the blood. Osteoblasts express both 25-hydroxylase as well as 1-α hydroxylase enzyme systems and can function as independent $1,25(OH)_2D$-producing cells [7]. The above calcium and phosphorus mobilizing action is at odds with the known mineralization promoting action of vitamin D. By enhancing the absorption of Ca^{2+} and PO_4^{3-} from the intestine and the renal tubules, vitamin D raises the concentrations of both Ca^{2+} and PO_4^{3-} in the blood and extracellular fluid. This increase in the calcium and phosphorus product results in net bone mineralization. Several studies have shown an association between 25(OH)D levels and rickets and bone mineral density [8].

Non-calcemic actions
It is estimated that~3 % of the human genome is regulated by $1,25(OH)_2D$ [9]. The genomic actions of vitamin D are mediated by the VDR which acts as a heterodimer with the retinoid X receptor (RXR). This heterodimer interacts with specific DNA sequences called vitamin D response elements (VDRE) within promoter region of target genes causing the activation or repression of gene transcription. This regulates two major cellular functions, proliferation and differentiation [10]. Many tissues such as the pancreatic islets, prostate; the colon; the breast; macrophages; malignant and immune cells and vascular smooth muscle cells, possess 1-α-hydroxylase and are capable of locally producing $1,25 (OH)_2D$ [11]. This has suggested a role for $1,25(OH)_2D$ in preventing cancers, modulating innate and adaptive immunity, affecting endocrine systems such as the renin-angiotensin-aldosterone axis and insulin release [3, 12]. Epidemiological evidence also associates vitamin D deficiency with cancer, autoimmune diseases, hypertension, and diabetes [3, 13].

Extra renal 1-α-hydroxylase activity is dependent on availability of substrate 25(OH)D and is not influenced by the hormones that control renal $1,25(OH)_2D$ production [14].

Vitamin D Deficiency in Pediatric CKD
There is no consensus as to what defines Vitamin D deficiency. The recent Institute of Medicine (IOM) guidelines recommend that levels>20 ng/ml are sufficient [15]. In normal adults PTH levels are elevated if 25(OH)D levels are less than 30–40 ng/ml and intestinal calcium transport is suboptimal below 25(OH)D levels of 32 ng/ml [16, 17]. So levels below 30 ng/ml may constitute vitamin D insufficiency and many experts believe that the current IOM recommended levels and doses are inadequate [18].

The Kidney Disease Outcome Quality Initiative (KDOQI) guidelines define 25 (OH) D deficiency as levels below 15 ng/ml, with levels between 16 to 30 ng/ml being considered as vitamin D insufficiency [19]. Multiple studies in adults with CKD have shown a high prevalence of 25 (OH) D deficiency, but there are very few, small pediatric prevalence studies [20–24]. Menon et al conducted a retrospective analyses of 57 pediatric CKD patients and found 77 % to have levels≤30 ng/ml. PTH was higher in those with deficiency and responded to ergocalciferol treatment [23]. Ali et al evaluated prevalence of 25 (OH)D deficiency in children with CKD in two different decades with different management guidelines. They showed a 20–75 % prevalence

of deficiency (≤15 ng/ml) in their patients from 1987–1996, with increasing deficiency as the decade progressed. In 2005–2006, after the KDOQI guidelines for 25 (OH)D supplementation became available, the prevalence of levels ≤15 ng/ml was still high at 33 % and 72 % of the 88 patients had levels less than 32 ng/ml. PTH levels had an inverse relationship to 25 (OH)D levels in their study [20].

Recently, Kalkwarf et al found 25(OH)D levels<20 ng/ml in half of the 182 patients (ages 5 to 21) with chronic kidney disease (stages 2 to 5). The risk of deficiency was significantly greater in advanced CKD. Focal segmental glomerulosclerosis, low albumin and high PTH levels were significantly associated with lower 25(OH)D levels [25].

The etiology of 25 (OH)D deficiency in CKD is multifactorial [26]. Poor nutrition and decreased consumption of vitamin D and calcium-rich foods are major reasons, as is the inability to participate in outside physical activity, thereby limiting sun exposure. Response to sunlight is also impaired in patients with CKD, as they are unable to produce vitamin D_3 in the skin even though the concentrations of provitamin D_3 in the epidermis are similar to age-matched controls [27]. Proteinuric renal diseases predispose to hypovitaminosis D due to urinary loss of vitamin D binding protein and vitamin D metabolites [28, 29]. A low calcium diet can also lead to low 25 (OH)D levels as the secondarily elevated PTH levels will cause a rapid degradation of 25 (OH)D to inactive metabolites. Secondary hyperparathyroidism worsens 25 (OH)D deficiency by promoting the activity of 24, 25-dihydroxylase enzyme and increasing degradation of 25 (OH)D [30].

$1,25(OH)_2D$ deficiency occurs as the kidney loses its ability to convert 25 (OH)D to $1,25(OH)_2D$. This is due to multiple reasons [3, 11]:
➢ Raised serum phosphate and FGF-23 down regulate renal 1-α hydroxylase [31]
➢ Suppression of 1-α hydroxylase due to uremia and acidosis
➢ Reduced availability of substrate 25 (OH)D and dependency of 1-α hydroxylase on substrate in CKD patients [6, 32]
➢ Reduced renal Megalin expression:- Megalin endocytosis of the 25 (OH)D-VDBP complex is essential for delivery of 25 (OH)D from the glomerular ultrafiltrate to the 1-α hydroxylase enzyme in the proximal tubule [33]

In addition, the biological activity of the available $1,25 (OH)_2D$ is lower in CKD patients due to less binding of VDR to the response element in the DNA within the uremic milieu [34].

Treatment of Vitamin D Deficiency
Earlier guidelines from KDOQI had recommended measuring 25(OH)D levels in stages 3–4 CKD only when the PTH levels were above the target range for stage of CKD. The most recent KDOQI and the KDIGO guidelines recommend measuring 25(OH)D levels once a year in children with CKD stages 2 to 5 [35, 36]. Supplementation is initiated if the levels are<30 ng/ml as per Table 1 [20].

Recommended supplementation for vitamin D deficiency/insufficiency in patients with CKD

Serum 25 (OH) D (ng/ml)	Definition	Dose of ergocalciferol/cholecalciferol	Duration
<5	Severe 25(OH) D deficiency	−8,000 IU/d orally or enterally for 4 wk or (50,000 IU/wk for 4 wk); followed by 4,000 IU/d or (50,000 IU twice per mo for 2 mo)	3 mo
5–15	Mild 25(OH) D deficiency	4,000 IU/d orally or enterally for 12 wk or (50,000 IU every other wk, for 12 wk)	3 mo
16–30	25 (OH) D insufficiency	2,000 IU daily or (50,000 IU every 4 wk)	3 mo

KDOQI guidelines do not make a distinction between using ergocalciferol (D2) vs. cholecalciferol (D3) as there is insufficient data to prove the superiority of one over the other. Studies in healthy adults have shown conflicting results. Holick et al in a randomized, placebo-controlled, double-blinded study of 68 healthy adults demonstrated no difference in 25 (OH)D levels when supplemented with 1000 IU vitamin D3 or 1000 IU vitamin D2, or 500 IU vitamin D2 plus 500 IU vitamin D3 daily [37]. Heaney et al, in a single blind randomized controlled trial in 33 healthy, Caucasian adults compared weekly 50,000 IU D2 vs. D3 and found higher peak 25 (OH)D levels and higher calciferol content in fat tissue in the cholecalciferol group [38]. There are no studies comparing ergocalciferol and cholecalciferol in children with CKD.

Doses required to maintain normal 25 (OH) D levels once repletion is achieved are not known. The 2008 KDOQI clinic practice guidelines for nutrition in children with CKD give a wide range of 200–1000 units daily as maintenance doses and recommend annual monitoring of levels [20]. The adequacy of these doses needs to be studied. Certain groups of children, especially those with proteinuric diseases and those living in northern latitudes, may need more frequent assessment of levels. Adolescents are notorious for non-compliance with medications and may need a more diligent follow up of levels.

There are very few small studies of vitamin D supplementation in pediatric CKD and all have used different dosing regimens of either ergocalciferol or cholecalciferol. Most of them have shown improvement in 25(OH)D levels and decrease in PTH levels post supplementation [21–23].

Recently Shroff et al tested the hypothesis that nutritional vitamin D (ergocalciferol) supplementation in children with CKD stages 2–4 delays the onset of secondary hyperparathyroidism in a randomized, double-blinded, placebo-controlled study in children with CKD 2–4. Forty-seven children were 25(OH)D-deficient and randomly assigned to receive ergocalciferol or placebo. Nine of 20 children on placebo and 3 of 20 children on ergocalciferol developed hyperparathyroidism (odds ratio, 4.64; 95 % confidence interval, 1.02–21.00). The time to development of hyperparathyroidism was significantly longer with ergocalciferol treatment compared with placebo (hazard ratio, 0.30; 95 % confidence interval, 0.09–0.93, P00.05). They concluded that ergocalciferol is an effective treatment that delays the development of secondary hyperparathyroidism in children with CKD 2–3 [39].

Calcitriol and alfacalcidol are widely used in children to suppress PTH levels. They have demonstrated efficacy when given in daily or intermittent doses [40, 41]. Newer vitamin D receptor activators (VDRA) have been developed to maximize affinity for parathyroid tissue, while minimizing the adverse effects of increased calcium and phosphorus absorption. Doxercalciferol (1α-hydroxyvitamin D_2) and paricalcitol (19-nor-1,25-dihydroxyvitamin D_2) are the two new VDRA's available in the United States. Doxercalciferol was found to be as effective as calcitriol in controlling PTH levels and suppressing bone formation rate in a randomized trial of 60 children on peritoneal dialysis. There was no difference in phosphorus levels between the two groups [42]. Paricalcitol decreased iPTH levels in children receiving hemodialysis with no significant changes in serum calcium, phosphorus, or Ca × P product in a double blind, placebo-controlled trial in pediatric patients on hemodialysis [43]. In a retrospective analysis comparing IV calcitriol and Paricalcitol, both were equally effective in lowering PTH. However, more episodes of elevated calcium × phosphorus product were seen in the calcitriol group [44].

Adverse Effects of Vitamin D
Active vitamin D can cause hypercalcemia and hyperphosphatemia. In dialysis patients $1,25(OH)_2D$ levels correlated with carotid artery intima media thickness (cIMT), carotid artery stiffness and carotid artery calcifications (CAC). cIMT and CAC scores were significantly higher at both low and high $1,25(OH)_2D$ levels [45]. This suggests a narrow therapeutic window for the use of these compounds.

Vitamin D and Growth
Growth failure in CKD is multifactorial. Renal osteodystrophy alters growth plate physiology. PTH levels required for normal growth are not well defined. Adynamic bone diseases as well as elevated PTH levels result in growth suppression.

Langman et al in a prospective study of 9 children with moderate CKD demonstrated a significant correlation between pre therapy and 1 y values of growth velocity and 25(OH)D concentrations. There was improvement in linear growth velocity from below 2 SD in the pre therapy year to normal range (+/− 2 SD) [**46**]. Chesney et al also showed increased growth after supplementation with $1,25 (OH)_2D$ for 26 mo in 6 preadolescent children with renal osteodystrophy [**47**]. Chan et al demonstrated improved growth velocity in pre pubertal children with severe CKD (GFR <20 ml/min) after 1,25-dihydroxyvitamin D treatment [**48**]. These were small non-randomized studies. The role of vitamin D in growth failure needs to be evaluated in large clinical trials.

Vitamin D and it Potential Renoprotective Actions
Vitamin D analogues can affect renal outcomes by affecting proteinuria, blood pressure and inflammation. Most of the clinical data for these outcomes is in adults.

Multiple animal models have suggested a role for active vitamin D in cardiac structure and function, albuminuria, and kidney fibrosis. The hemodynamic and proinflammatory actions of the activated renin angiotensin aldosterone system (RAAS) have been shown to play an important role in the progression of CKD, $1,25(OH)_2D$ being negative regulator of this system [12]. The vitamin D receptor knockout mice develop elevated BPs and left ventricular hypertrophy [18], which occurs due to a rise in renin consequent to loss of normal suppression of the renin-angiotensin system by vitamin D [19]. In rats with spontaneous hypertension, treatment with vitamin D analogs ameliorates left ventricular hypertrophy and improves left ventricular diastolic measures [20]. Mizobuchi et al showed that combined therapy with enalapril and paricalcitol significantly decreased proteinuria, glomerulosclerotic index, and tubulointerstitial volume in uremic rats [49].

Vitamin D and Proteinuria
There are now a few randomized control trials in adults that have evaluated the effect of active vitamin D therapy on albuminuria [50, 51]. Agarwal et al in a double-blind, randomized, placebo-controlled trial evaluated the safety and efficacy of oral Paricalcitol. CKD Stage 3–4 patients with secondary hyperparathyroidism were randomized to oral Paricalcitol or placebo and followed for 24 wk. Patients on Paricalcitol (regardless of age, sex, race, diabetes mellitus, hypertension, or use of ACEI/ARB) were more likely (OR=3.2, 95 % CI 1.5–6.9) to have reduction of proteinuria [52].

The VITAL study, a large, randomized placebo controlled trial of Paricalcitol (1 and 2 µg) in 281 subjects with type 2 diabetes and proteinuria showed significant reduction in urine albumin creatinine ratios with a dose dependent reduction in proteinuria when compared to placebo [53].

Vitamin D and Blood Pressure
Observational studies have shown an association between lower 25(OH)D levels and incident hypertension in the non-CKD population [54]. The VITAL study described above also showed that BP was significantly lower in the participants randomized to the 2 µg dose by a mean of approximately 8 mmHg [53]. There is only one pediatric study that compared the effect of a $2 \mu g/m^2$ dose of IV 1,25-dihydrocholecalciferol in 7 children on hemodialysis and 7 healthy controls. Children on dialysis showed normalization of BP and insulin sensitivity [55].

Vitamin D and Progression of Chronic Kidney Disease
Epidemiological studies have shown low 25(OH)D and $1,25(OH)_2D$ levels to be independent predictors of disease progression and death in patients with CKD and End Stage Renal Disease (ESRD) [56, 57].

Melamed et al evaluated the contribution of low 25(OH) D levels to the incidence of ESRD using data from the Third National Health and Nutrition Examination Survey-linked Medicare claims files. 25(OH)D levels<15 ng/ml were associated with increased risk for ESRD after multivariable adjustment [58]. Ravani et al followed 168 adult Caucasian patients with CKD for 6 y. Forty eight started dialysis and 68 died after average follow up of 4 y. 25(OH)D predicted both time to death and end-stage renal disease on crude as well as after multivariable adjustment [59].

Use of activated vitamin D has been associated with slower progression of chronic kidney disease and improved survival in adult CKD and ESRD patients [60–62]. There are no pediatric studies that have evaluated the association of CKD progression with vitamin D levels or activated vitamin D use.

Vitamin D and Cardiovascular Effects in CKD
Experimental studies suggest that active vitamin D analogues at low doses protect against aortic calcification, prevent cardiac/vascular remodeling, reverse LVH, ameliorate myocardial renin over expression and lower blood pressure [63, 64].

However, recently reported results of the PRIMO trial, a randomized double blinded study of CKD 3–4 subjects, investigating effects of oral paricalcitol compared to placebo on LVMI, failed to show any reduction in left ventricular mass after 48 wk of treatment.

Patange et al explored the relationship between parameters of calcium–phosphorus metabolism including 25(OH)D and arterial wall stiffness in 43 pediatric patients with CKD/ESRD, who had no history of underlying congenital or structural cardiac disease. Multiple regression analysis showed that 25(OH)D was the only significant independent predictor of increased central arterial stiffness in the subgroup of children receiving hemodialysis [65].

Vitamin D and Inflammation
Uremia is a state of chronic inflammation and preclinical data suggests active vitamin D decreases inflammatory biomarkers [66, 67].

Alborzi et al evaluated change in hsCRP in a randomized controlled trial of 24 patients, allocated to placebo,1 and 2 µg of Paricalcitol. The CRP levels showed a 50 % increase in the placebo group and a decrease of 20 and 30 % in the 1 and 2 µg groups respectively [51].

Kalkwarf et al evaluated 182 patients (ages 5 to 21) with CKD stages 2 to 5 and found 33 % of them had 25(OH)D levels <20 ng/ml. The lower 25(OH)D levels were associated with higher levels of inflammatory markers (C-reactive protein and IL-6), despite adjusting for the severity of kidney disease [25].

Vitamin D Supplementation in CKD
The big unanswered question is whether to supplement with active or nutritional vitamin D. 25(OH)D concentrations are 1000 times higher than $1,25(OH)_2D$ and may overcome VDR resistance seen in uremia. Local extrarenal calcitriol production is substrate dependent and requires sufficient levels of 25(OH)D for paracrine actions. However at GFR<50 ml/min, active vitamin D compounds are also needed. $1,25(OH)_2D$ facilitates cellular uptake of 25 (OH)D in uremic states by enhancing megalin expression. It seems that combined use of nutritional and activated vitamin D may be synergistic for both the classic and non-classical actions. However, combined use of these agents needs to be studied for dosage and potential toxicity.

Conclusions
Vitamin D deficiency is highly prevalent in CKD. Correction of 25(OH)D deficiency may prevent early secondary hyperparathyroidism. Dosage guidelines for 25(OH)D

deficiency management in children are opinion based. Normal 25(OH)D levels in late CKD are desirable to provide adequate substrate for the paracrine, non calcemic actions of $1,25(OH)_2D$. Active vitamin D compounds for treatment of secondary hyperparathyroidism have to be used judiciously to prevent cardiovascular complications.

Prospective studies such as CKiD and 4 C should help to evaluate the role of vitamin D insufficiency/deficiency in growth failure, progression of chronic kidney disease and cardiovascular outcomes. Randomized clinical trials are needed to define the dosage and monitoring guidelines for treating vitamin D deficiency, optimum PTH levels for growth and to compare the effectiveness of different vitamin D receptor agonists.

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