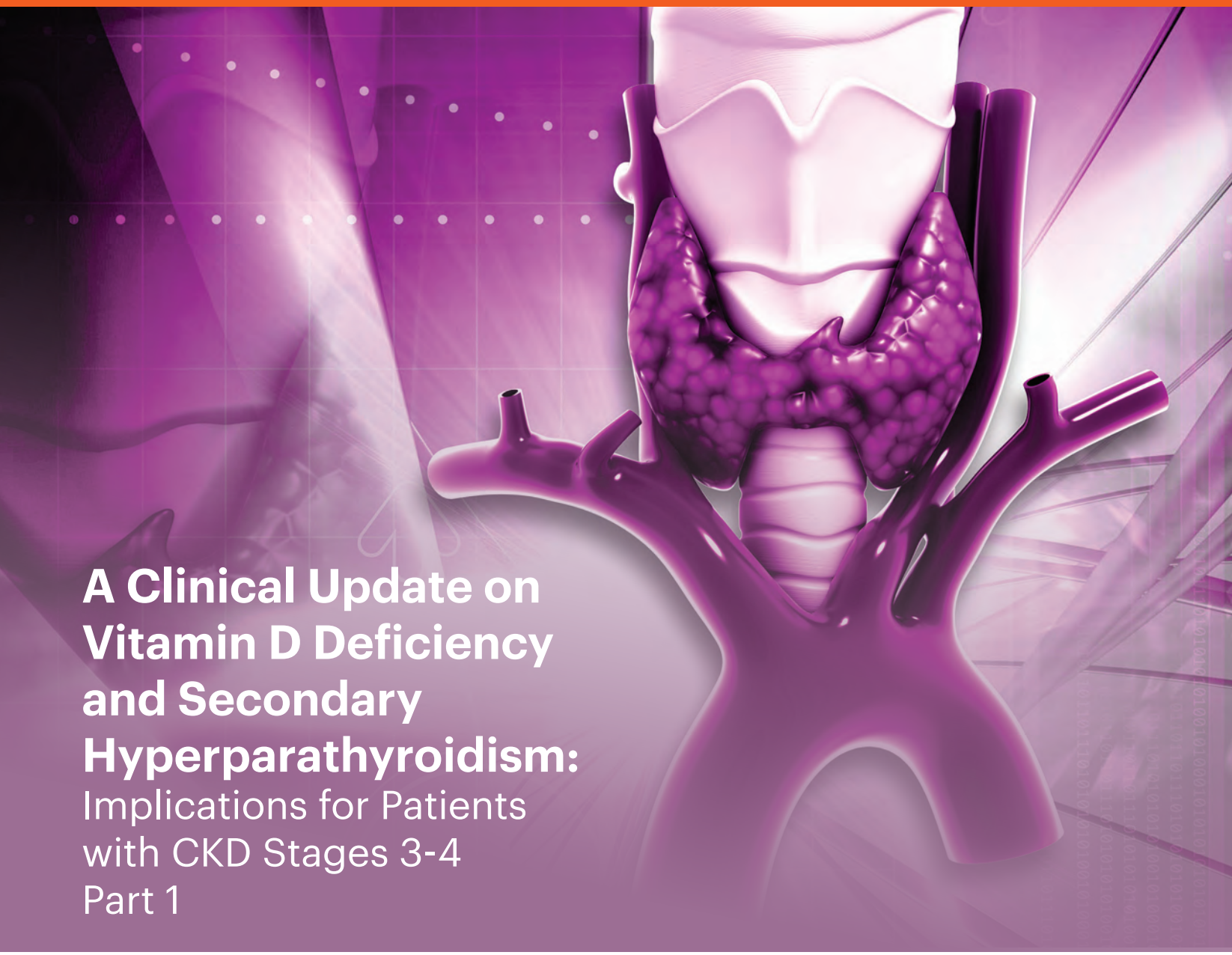


A Clinical Update on Vitamin D Deficiency and Secondary Hyperparathyroidism:

Implications for Patients with CKD Stages 3-4

Part 1

National Kidney Foundation®

INTRODUCTION

Studies confirm that the prevalence of vitamin D deficiency and insufficiency is greater across the stages of chronic kidney disease (CKD) than in the general population.[1–3] Although there is currently no consensus in the medical community regarding optimal levels in CKD or the general population, vitamin D deficiency has been defined as 25(OH)D concentration <20 ng/mL, and insufficiency has been defined as 25(OH)D concentration <30 ng/mL.[4,5] In CKD stages 3 and 4, up to two-thirds of patients are reported to have vitamin D insufficiency. In CKD stage 5, up to 97% of patients have vitamin D insufficiency.[3,6,7] The significance of these findings in CKD is related to the association of vitamin D deficiency and secondary hyperparathyroidism (SHPT), which contributes to the development of bone disease, vascular calcification, and increased morbidity and mortality.

Vitamin D Physiology and Nomenclature

Vitamin D is found in nature as vitamin D_2 (ergocalciferol) derived from plant sources, and vitamin D_3 (cholecalciferol), derived from animal sources (Table 1). Vitamin D_3 is produced mostly by skin exposure to ultraviolet B (UVB) light.[8] In the skin, 7-dehydrocholesterol is converted to previtamin D_3 with UVB exposure. Previtamin D_3 then thermally isomerizes to become vitamin D_3. Cutaneous vitamin D synthesis by sunlight is influenced by zenith angle, skin pigment, temperature, and aging.[9] Incidental UVB light exposure is about 50% of the amount required to cause mild sunburn, also known as minimal erythemal dose (MED).[9] Exposure of approximately 20% of body surface area to an amount of UVB light equal to 0.5 MED is equivalent to a dietary intake of approximately 1,400-2,000 IU of vitamin D_3.[9]

Few foods contain vitamin D naturally, including fatty fish, fish liver oils, and egg yolk. The main dietary sources are foods fortified with vitamin D and dietary supplements. Ingested vitamin D becomes incorporated into chylomicrons and is then transported through the lymphatic system for venous circulation.[10] Vitamin D that is produced in skin or obtained from the diet is stored in and released from adipose tissue.

Vitamin D (ergocalciferol or cholecalciferol) is converted to a hormone, known as $1,25(OH)_2D$, in a two-step process involving the liver and the kidney. In the liver, vitamin D undergoes the first hydroxylation at the carbon-25 position by the cytochrome P450 enzyme CYP2R1 to form 25(OH)D, which circulates in the blood bound to vitamin D-binding protein.[11] This metabolite is the main storage form of vitamin D, and is the clinical indicator used to assess vitamin D status.

In the proximal renal tubule, the 25(OH)D undergoes a second hydroxylation at the carbon-1 position by the cytochrome P450 1α-hydroxylase (CYP27B1) to form $1,25(OH)_2D$, the biologically active form of vitamin D (Table 1).[11] Renal production of $1,25(OH)_2D$ is stimulated by parathyroid hormone (PTH), and inhibited by increasing concentrations of fibroblast growth hormone 23 (FGF23). In addition to regulated hydroxylation in the kidney, 25(OH)D can be converted to $1,25(OH)_2D$ by many other tissues in the body. While this local cellular production adds little to the circulating concentrations of $1,25(OH)_2D$, it may have a role in regulating cell growth as well as immune function.

Vitamin D Metabolism and Catabolism in CKD

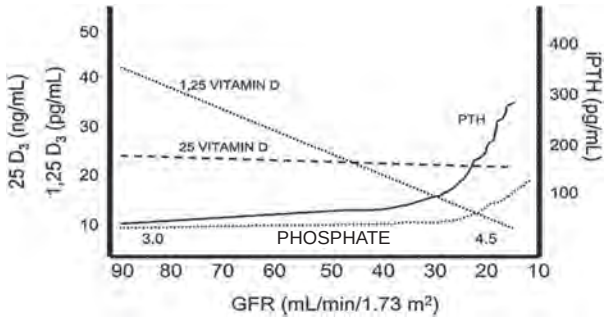
The overall prevalence of vitamin D insufficiency in the U.S. is greater than 40%, being as high as 80% in the Black/African American population.[12] Thus, vitamin D deficiency and insufficiency are noted early in CKD.[1] Serum 25(OH)D concentrations often fall below 30 ng/mL in CKD stage 2 before reductions are seen in $1,25(OH)_2D$ concentrations. Reductions in 25(OH)D concentrations occur independently of changes in glomerular filtration rate (GFR) and reduced concentrations are present across the spectrum of CKD.[13] These changes occur before increases in serum phosphate are evident. (Figure 1)

Table 1. Vitamin D Nomenclature

Collective terminology	Vitamin D_2 and metabolites	Vitamin D_3 and metabolites
Parent compound: **Vitamin D** (from diet or UVB light)	Vitamin D_2 (plant sources) Ergocalciferol	Vitamin D_3 (animal sources) Cholecalciferol
Product of 1st hydroxylation: **25-Hydroxyvitamin D** **25(OH)D** **(Vitamin D Pro-Hormone)**	25-Hydroxyvitamin D_2 $25(OH)D_2$ Ercalcidiol	25-Hydroxyvitamin D_3 $25(OH)D_3$ Calcidiol Calcifediol
Product of 2nd hydroxylation: **1,25-Dihydroxyvitamin D (active)** **$1,25(OH)_2D$** **(Vitamin D Hormone)**	1,25 Dihydroxyvitamin D_2 $1,25(OH)_2D_2$ Ercalcitriol	1,25 Dihydroxyvitamin D_3 $1,25(OH)_2D_3$ Calcitriol

Adapted from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. *Kidney Int*. 2009;76: S1–S130.

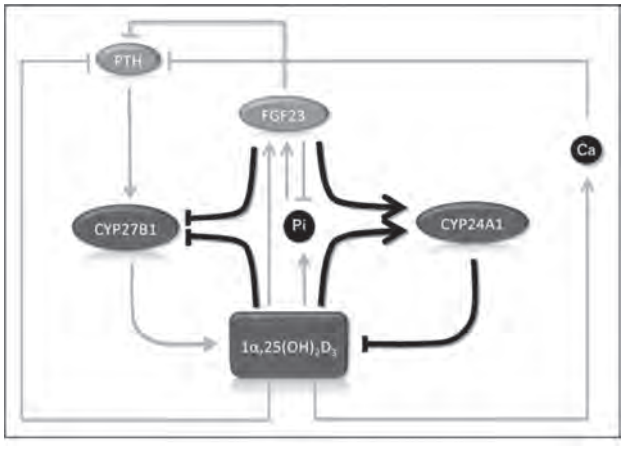
Figure 1. Changes in Vitamin D Metabolism in CKD



Gal-Moscovici A, et al. *J Bone Miner Res.* 2007;Suppl 2:V91-V94

Some reasons for vitamin D deficiency and insufficiency in CKD include reduced UVB light exposure, impaired vitamin D_3 production in the skin, obesity, minority race/ethnicity, reduced intake of vitamin D-rich foods, and loss of DBP in the urine due to proteinuria. As CKD progresses, elevated FGF23 upregulates cytochrome P450 enzyme CYP24A1 and downregulates CYP27B1, which together contribute to reduced circulating levels of $1,25(OH)_2D$. CYP24A1, expressed in cells containing the vitamin D receptor (VDR), catalyzes the conversion of 25(OH)D and $1,25(OH)_2D$ into 24-hydroxylated metabolites that are excreted (Figure 2).[14–17] Renal production of $1,25(OH)_2D$ is further limited by uremic and acid milieus, hyperphosphatemia, and reduced endocytotic uptake of $25(OH)_2D$ by megalin and cubulin.[18–20]

Figure 2. Vitamin D Catabolism in CKD



Petkovich M, et al. *Curr Opin Nephrol Hypertens.* 2011;20:337-344.

Vitamin D resistance also plays a role in altered vitamin D metabolism in CKD. In advanced CKD, $1,25(OH)_2D$ resistance occurs due to progressive loss of VDR in the parathyroid gland, impaired binding of $1,25(OH)_2D$ to VDR due to low $1,25(OH)_2D$ concentrations, and impaired binding of vitamin D-VDR complex to the VDR response element.[15] The combination of insufficient vitamin D production, accelerated vitamin D catabolism, and vitamin D resistance contribute to $1,25(OH)_2D$ deficiency and insufficiency.

Central Role of Vitamin D in Secondary Hyperparathyroidism

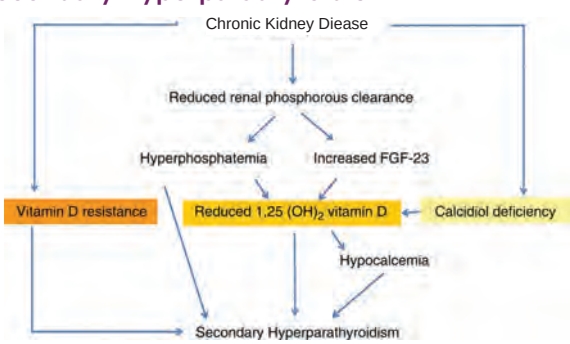
Vitamin D plays a key role in regulating mineral and bone metabolism. Adequate concentrations of $1,25(OH)_2D$ are needed for normal bone formation and mineralization.[1,21] The key target organs of $1,25(OH)_2D$ include bone, gastrointestinal tract, kidneys, and parathyroid gland:

- Bone — $1,25(OH)_2D$ stimulates osteoclasts to release calcium into the circulation
- Small intestine — $1,25(OH)_2D$ stimulates absorption of calcium and phosphorus
- Kidney — $1,25(OH)_2D$ along with PTH stimulates calcium absorption from the renal distal tubule
- Parathyroid gland — $1,25(OH)_2D$ feeds back to suppress synthesis and secretion of PTH

The development of SHPT is caused by a pathological sequence of events: elevated FGF23 triggers a reduction of $1,25(OH)_2D$ and calcium concentrations, resulting in increased synthesis and secretion of PTH.[15] Vitamin D insufficiency can further exacerbate deficiency of $1,25(OH)_2D$ and elevated FGF23 induced by CKD. (Figure 3) SHPT affects 40-80% of patients with stage 3 or 4 CKD and 95% of patients with stage 5 CKD.[3,6]

Increased secretion of FGF23 from osteocytes is one of the earliest detectable abnormalities in mineral metabolism with advancing kidney disease. As GFR declines, FGF23 concentrations rise progressively, with studies showing significant increases during CKD stages 2 to 3.[22] Increased FGF23 leads to suppression of $1,25(OH)_2D$ concentrations, resulting in feedback inhibition failure of the parathyroid glands, gland growth, and PTH secretion. There is also reduced dietary calcium absorption because of $1,25(OH)_2D$ deficiency. The progressive loss of $1,25(OH)_2D$ production and hypocalcemia leads to a rise in PTH concentrations beginning approximately at GFR 45 ml/min/1.73m^2.[2,6,23] Prolonged elevation of PTH causes excessive calcium and phosphate to be released from bone, eventually leading to bone disease, and perhaps increased risks of vascular calcification, morbidity, and mortality.[24] In a study of patients with CKD, vitamin D deficiency (defined as 25(OH) D < 15 ng/ml) and SHPT were associated with increased mortality.[25]

Figure 3. Role of Vitamin D in the Pathogenesis of Secondary Hyperparathyroidism



Nigwekar SU, et al. *Bonekey Rep.* 2014 Feb 5;3:498.

Vitamin D and Other Chronic Diseases

The VDR is found in a variety of cells throughout the body including bone marrow, immune system, skin, breast and prostate epithelial cells, muscle, and intestine. These extra-renal sites also have the capacity to express CYP27B1 and produce their own supply of $1,25(OH)_2D$ from 25(OH)D.[26] Extra-renal synthesis of $1,25(OH)_2D$ is reduced or interrupted by vitamin D deficiency and insufficiency. Therefore, correction of vitamin D deficiency and insufficiency may have a potential role in the prevention and treatment of many chronic diseases such as diabetes, chronic infections, hypertension, and cardiovascular disease, although definitive proof awaits necessary randomized trials.[26]

SUMMARY

Vitamin D deficiency and insufficiency develop early in CKD and prevalence increases as CKD progresses, reaching a level that is greater than in the general population. PTH and FGF23 regulate $1,25(OH)_2D$ production independently. The activation of vitamin D requires a 2-step hydroxylation process involving the liver and kidney. In the kidney, CYP27B1 mediates the final hydroxylation to form $1,25(OH)_2D$, the active hormonal form of vitamin D. As kidney function declines, the activity of CYP27B1 in the kidney is suppressed resulting in lower circulating $1,25(OH)_2D$. The mechanism responsible for lower $1,25(OH)_2D$ concentrations in early-stage CKD is elevated FGF23[15]. Vitamin D insufficiency can further exacerbate deficiency of $1,25(OH)_2D$ and elevated FGF23 induced by CKD. Reduced concentrations of $1,25(OH)_2D$ play a key role in promoting SHPT and resulting bone disease, and perhaps also contribute to calcification of cardiovascular tissues. SHPT affects 40-80% of patients with stage 3 or 4 CKD and 95% of patients with Stage 5 CKD. CKD patients should be monitored for SHPT and effectively treated for underlying vitamin D deficiency in order to control SHPT and potentially reduce morbidity. Since vitamin D receptors are found in a variety of cells throughout the body, vitamin D deficiency and insufficiency may also play a role in other chronic diseases.

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