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. Extra-renal synthesis of 1,25(OH)2D is reduced or interrupted. 

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**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. FPTH 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. Vitamin D insufficiency can further exacerbate deficiency of 1,25(OH)2D and elevate 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.

References

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. 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 <30 ng/mL, and insufficiency has been defined as 25(OH)D concentration 30-49 ng/mL. 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. 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$_2$ is produced mostly by skin exposure to ultraviolet B (UVB) light, but in the skin, 7-dehydrocholesterol is converted to previtamin D$_3$, then thermally isomerizes to become vitamin D$_3$. Cutaneous vitamin D synthesis by sunlight is influenced by zenith angle, skin pigment, and is estimated to become vitamin D$_3$. Cutaneous vitamin D synthesis of approximately 1,400-2,000 IU of vitamin D$_3$. UVB light equal to 0.5 MED is equivalent to a dietary intake of 25(OH)D concentration <20 ng/mL, and insufficiency is greater across the stages of chronic kidney disease, vascular calcification, and perhaps increased risks of vascular calcification, morbidity, and mortality.

**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. Thus, vitamin D deficiency and insufficiency are noted early in CKD. Serum 25(OH)D concentrations often fall below 30 ng/mL in CKD stage 2 before reductions are seen in 1,25(OH)$_2$D 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. This change occurs before increases in serum phosphate are evident. (Figure 1)

**Figure 1. Changes in Vitamin D Metabolism in CKD**

Vitamin D plays a key role in regulating mineral and bone metabolism. Adequate concentrations of 1,25(OH)$_2$D are needed for normal bone formation and mineralization. The key target organs of 1,25(OH)$_2$D include bone, gastrointestinal tract, kidneys, and parathyroid gland.

- **Bone** — 1,25(OH)$_2$D stimulates osteoclasts to release calcium into the circulation
- **Small intestine** — 1,25(OH)$_2$D stimulates absorption of calcium and phosphorus
- **Kidney** — 1,25(OH)$_2$D along with PTH stimulates calcium absorption from the renal distal tubule
- **Parathyroid gland** — 1,25(OH)$_2$D 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)$_2$D and calcium concentrations, resulting in increased synthesis and secretion of PTH. Vitamin D insufficiency can further exacerbate deficiency of 1,25(OH)$_2$D 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.

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. Increased FGF23 leads to suppression of 1,25(OH)$_2$D 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)$_2$D deficiency. The progressive loss of 1,25(OH)$_2$D production and hypocalcemia leads to a rise in PTH concentrations beginning approximately at GFR 45-50 ml/min/1.73 m$^2$. 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. 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.

**Central Role of Vitamin D in Secondary Hyperparathyroidism**

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**Figure 2. Vitamin D Catabolism in CKD**
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. 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. 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. 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.

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Vitamin D Metabolism and Catabolism in CKD

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Vitamin D Metabolism and Catabolism in CKD

Some reasons for vitamin D deficiency in CKD include reduced UV light exposure, impaired vitamin D 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). Renal production of 1,25(OH)2D is further limited by uric acid and acid mideus, hyperphosphatemia, and reduced endocytotic uptake of 25(OH)D by megalin and cubulin. (Figure 2)

Figure 2. Vitamin D Catabolism in CKD

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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 mechanisms responsible for lower 1,25(OH)2D concentrations in early-stage CKD is elevated FGF23. 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.

References