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Chapter 2

Vitamin D and Renal Disease

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Abstract

The metabolism of vitamin D (VD) is severely impaired in chronic kidney disease (CKD). Uremia is not only associated with the reduction of its active form 1,25-dihydroxyvitamin D but also in the reduction of all VD metabolites. CKD-associated abnormalities in VD are part of the CKD-related mineral-bone disease. However, VD has beneficial effect on the kidneys due to its pleiotropic effects, namely, antiproteinuric effect and renin-angiotensin-aldosterone system suppression, thus making the relationship between VD and the kidney even more complicated. The aim of our chapter is to reveal the changes in vitamin D axis in CKD, to outline the possible beneficial effects of vitamin D in renal patients, including end-stage renal patients and kidney transplant recipients, and to address the current opinions concerning treatment with cholecalciferol, calcitriol, and vitamin D analogs.

Keywords: vitamin D, chronic kidney disease, mineral bone disease, kidney transplantation, pleiotropic effects

1. Introduction: vitamin D and calcium-phosphorus metabolism in the healthy kidney

The kidney plays a pivotal role in vitamin D (VD) metabolism. In the proximal tubules the enzyme 1a hydroxylase (CYP27B1) transforms 25-hydroxyvitamin D into the active metabolite 1,25-hydroxyvitamin D (Figure 1). 25-hydroxyvitamin D (25VD) is absorbed in the proximal tubule cells via megalin-dependent pathway. The absorption, however, is severely impaired in nephrotic syndrome [1].
CYP27B1 activity is influenced by different factors. Parathyroid hormone (PTH), prolactin, human growth hormone, low serum calcium, and phosphorus increase CYP27B1 activity, whereas 1,25-dihydroxyvitamin D, thyroid hormones, metabolic acidosis, and fibroblast growth factor-23 (FGF-23) suppress its activity [2–4]. The proximal tubules are the major site for activation of vitamin D (VD). However, nonrenal CYP27B1, transforming 25VD into 1,25VD, was detected in other tissues—skin (basal keratinocytes, hair follicles), lymph nodes (granulomata), colon (epithelial cells and parasympathetic ganglia), pancreas (islets), adrenal medulla, brain (cerebellum and cerebral cortex), and placenta (decidual and trophoblastic cells) [5]. Together with the widely distributed vitamin D receptor (VDR) in human body, these data are the basis of the suggested pleiotropic effects of VD. Of utmost importance for the nephrologist are the renoprotective properties of vitamin D, which are based on renin-angiotensin-aldosterone system suppression, nucleotide factor-kB downregulation, Wnt/β-catenin pathway suppression, and upregulation of slit diaphragm protein synthesis [6–8].

**Figure 1.** Vitamin D synthesis.
The kidney is crucial in maintaining calcium-phosphorus metabolism. Apart from activation of VD, the kidneys increase calcium and phosphorus reabsorption in the tubules under the influence of 1,25-dihydroxyvitamin D (1,25VD). Furthermore, 1,25VD is involved in osteoclast activation and differentiation, as well as osteoblast activation thus taking part in bone remodeling. In addition, the proximal tubules are the target of major phosphatoninns, such as FGF-23 (by α-klotho-dependent mechanism) and PTH [9]. The basic interactions of the kidney in the mineral bone metabolism are shown in Figure 2.

A particular attention should be paid to FGF-23 and klotho pathways, as their discovery have changed significantly our knowledge of bone health and changes in calcium-phosphorus metabolism in chronic kidney disease (CKD). Fibroblast growth factor-23 is an osteoblast-/osteocyte-secreted hormone with primary physiological effects on the kidney and the parathyroid gland. FGF-23 stimulates phosphaturia by downregulating luminal expression of sodium-phosphate cotransporters in the proximal tubule and reduces systemic levels of 1,25VD by inhibiting renal 1-α hydroxylase and stimulating the catabolic 24-hydroxylase [10, 11] (Figure 3).
In healthy subjects, FGF-23 suppresses PTH secretion [12]. In addition, extrarenal effects have been described on cardiovascular system and brain [13]. Alfa-klotho is a protein cofactor for FGF-23 signaling, as it forms complexes with FGF-23 receptor, thus increasing its affinity for the hormone [14]. A soluble klotho was also detected, functioning as humoral factor. Soluble klotho downregulates insulin-like growth factor I, thus exerting antiaging properties [15]. It also potentiates 1,25VD-associated renal calcium absorption [16]. Furthermore, soluble klotho causes hypophosphatemia and phosphaturia independently of FGF-23 and is regarded as an early marker of CKD [17, 18].

In summary, the kidney is closely linked to the VD axis and calcium-phosphorus homeostasis. Early changes in renal function are associated with significant changes in VD metabolism. We shall start with VD pathology in patients with renal disease and at the end of our review the topic vitamin D metabolism after kidney transplantation will be discussed.

2. Vitamin D metabolism in kidney disease: pathophysiology

2.1. Chronic kidney disease: definition

According to the widely accepted definition by the international foundation for Kidney Disease/Improving Global Outcomes (KDIGO), chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health [19] (Table 1).
Markers of kidney damage (one or more)

- Albuminuria (AER ≥ 30 mg/24 hours; ACR ≥ 30 mg/g [≥3 mg/mmol])
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

Decreased GFR

GFR < 60 ml/min/1.73 m² (GFR categories G3a–G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; AER, albumin excretion rate; ACR, albumin:creatinine ratio.

Table 1. Criteria for CKD (either of the following for more than 3 months) [19].

CKD is a global health problem, affecting up to 10% of the population [20]. As the glomerular filtration rate (GFR) declines, especially below 60 ml/min/1.73 m², the ability of the kidney to excrete phosphate is diminished, leading to disruption of calcium-phosphorus homeostasis, pathological changes in hormone levels (PTH, FGF-23), and decrease in the level of VD metabolites. Subsequently, changes in bone morphology and extraskeletal calcifications occur. The changes in biochemical indicators, bone morphology, and extraskeletal calcium deposits are defined as chronic kidney disease-mineral bone disorder (CKD-MBD), Table 2. This is a new definition that clearly states the difference from renal osteodystrophy, taking into consideration a broader problem in CKD patients [21].

Table 2. KDIGO classification of CKD-MBD and renal osteodystrophy [21].
2.2. Changes in vitamin D and its metabolites

Changes in vitamin D metabolism are detected in the early stages of CKD in patients with GFR below 60 ml/min/1.73 m² [22]. Furthermore, the expression of the vitamin D receptor in CKD patients is suppressed [23]. These abnormalities are part of the biochemical component of CKD-related mineral bone disease, together with changes in PTH, bone alkaline phosphatase, serum levels of calcium, and phosphate.

2.2.1. Change in 1,25-dihydroxyvitamin D

The classical theory stated that the fall in the active VD metabolite is due to the initial kidney damage, thus leading to reduced calcium and phosphorus intestinal absorption and rise in PTH. With the discovery of FGF-23 and alfa-klotho axis however new explanation of the biochemical abnormalities appeared. Kidney damage leads to reduced ability of the tubules to eliminate phosphorus. This leads to rise in FGF-23 level in order to keep the phosphate level within normal limits. The rise of FGF-23, however, is the initial signal for suppressing renal 1-α hydroxylase and reducing 1,25VD. In addition, it leads to increased catabolism due to activation of 24-hydroxilase. FGF-23 starts to rise in patients GFR below 60 ml/min/1.73 m², keeping phosphate serum levels within normal limits well below this cut-off value [24].

To sum up, changes in hormones (PTH and FGF-23) and 1,25VD occur in the early stages of CKD, whereas deviations in calcium and phosphate are characteristic for the advanced CKD cases.

2.2.2. 25-Hydroxyvitamin D (25VD)

25-Hydroxyvitamin D is generally accepted marker for assessing vitamin D status due to its stable serum level and long half-life. Though there is no clear consensus on the definition of VD insufficiency, most of the studies define VD deficiency as 25VD level below 25 nmol/l, whereas insufficiency is defined as 25VD level between 25 and 80 nmol/l. Unfortunately, no clear definition for optimal 25VD level exists though some researchers define it as VD associated with normal PTH value in the general population or VD value above which there is no decrease in PTH [25–27]. Suboptimal levels are widely spread in CKD with prevalence peaking up to 92% in patients on hemodialysis [28]. Several factors can explain the low 25VD level in CKD (Table 3).

Poor VD status has been associated with a lot of complications and diseases, apart from its link to the calcium-phosphate homeostasis. Higher mortality was detected in the general population and in CKD patients with low 25VD [28]. Poor 25VD was also associated with higher risk for cancer, diabetes mellitus, hypertension, and depression in humans [29]. VDR was detected in malignant cells too. Activation of VDR in these cells was found to block the cell cycle or cause cell apoptosis [30]. Increased sun exposition had inverse correlation with prevalence of several malignancies [31]. Vitamin D increases insulin secretion and improves insulin resistance in diabetes. In addition, insulin receptor synthesis is improved, as well as systemic inflammation is reduced, which probably explains the positive effect of VD in animal models.
and human studies. Vitamin D supplementation in early infancy/or prior to birth was found effective in reducing the prevalence of diabetes type 1 [32]. Several mechanisms have been proposed for the influence of VD on blood pressure—suppression of renin-angiotensin system, calcium ion influx control in smooth muscle cells of the vessels, and improved activity of nitric oxide (NO). Indeed, several cross-sectional studies show that poorer VD status is associated with higher blood pressure values and higher prevalence of hypertension [33]. Several studies indicate that vitamin D insufficiency is linked with higher incidence of depression, without any data for the severity of the disease. There are several possible mechanisms for this relationship—VD may play important role in brain signaling and neuroimmunomodulation, as brain VDR were detected; in addition, vitamin D takes part in serotonin synthesis [34].

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Advanced patient's age</td>
<td>Reduced skin synthesis of cholecalciferol</td>
</tr>
<tr>
<td>Dietary restrictions in CKD</td>
<td>Reduced oral intake</td>
</tr>
<tr>
<td>Uremia</td>
<td>Reduced skin synthesis of cholecalciferol</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Increased urine loss</td>
</tr>
<tr>
<td>Higher prevalence of African race in CKD</td>
<td>Reduced skin synthesis of cholecalciferol</td>
</tr>
<tr>
<td>Higher prevalence of obesity</td>
<td>Reduced bioavailability of 25VD</td>
</tr>
</tbody>
</table>

Abbreviations: 25VD, 25-hydroxyvitamin D; CKD, chronic kidney disease.

Table 3. Determinants for lower 25-hydroxyvitamin D levels in CKD.

Further studies are needed to clarify the potential extraskeletal effects of VD in CKD, including larger randomized controlled trials (RTC). The clinical implications of impaired VD status and the possible treatment options in renal patients will be discussed later in this chapter.

2.2.3. The vitamin D receptor in CKD

1,25-Dihydroxyvitamin D mediates its effects via the vitamin D receptor (VDR). It is a nuclear peptide, belonging to a superfamily of nucleotide receptors, like the receptors for retinoic acid and the thyroid hormones. As 1,25VD is the active VD metabolite, VDR has almost 1000 times higher affinity for it than for other VD metabolites. However, the receptor can be activated by 25VD too in cases of toxic VD levels above 370 nmol/l. VDR is expressed in almost all the tissues in human body, with highest expression, however, in intestines, parathyroid gland, and bones. Once 1,25VD binds to VDR, the complex forms a heterodimer with the receptor for retinoid X (RXR) within the nucleus. The 1,25VD-RXR complex binds to vitamin D reacting elements, activating or suppressing genes.

Activation of VDR leads to increased calcium intestinal absorption, suppression of PTH synthesis in parathyroid gland, and modulation of osteoblast and osteoclast activity. However, due to its wide distribution, it is believed that VDR plays a more complicated role in human health, apart from controlling mineral homeostasis. Furthermore, VDR can be located in the
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