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Chapter

Vitamin D Deficiency in Renal Disease

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Abstract

Vitamin D deficiency is highly prevalent in patients with renal disease. The abnormal vitamin D (VD) metabolism in chronic kidney disease (CKD) is a key factor for developing CKD-related mineral bone disease (CKD-MBD), which directly influences the survival of the CKD patients. The importance of VD is perhaps of greater value due to its pleiotropic effects that span beyond calcium-phosphorus metabolism (cancer protection, diabetes prevention, and renal protection). The aim of our chapter is to depict the clinical implications of VD deficiency in the setting of CKD, including VD pleiotropy in renal disease, and to propose the most adequate treatment suggested in the literature.

Keywords: vitamin D deficiency, chronic kidney disease, mineral bone disease, vitamin D pleiotropy, vitamin D supplementation

1. Introduction

Vitamin D (VD) deficiency is a growing problem worldwide [1]. Due to the wide distribution of the vitamin D receptor in human body, the effect of VD spans beyond calcium-phosphorus and bone metabolism—VD deficiency is associated with higher prevalence of hypertension, diabetes mellitus, and neoplasia [2]. As kidneys play an important role in the metabolism of VD, patients with chronic kidney disease (CKD) are at increased risk for VD deficiency. The aim of our chapter is to demonstrate the clinical implications of vitamin D deficiency in CKD and to outline the possible treatment options in this group of patients. In our review, a stress is laid on clinical trials due to their greater relevance to everyday clinical practice, compared to *in vitro* and animal models.

2. Definition: vitamin D deficiency, vitamin D sufficiency, chronic kidney disease

VD status is being evaluated via the serum level of 25-hydroxyvitamin D (25VD)—the metabolite formed in the first hydroxylation in the liver, due to its longer half-life (approx. 3 weeks), compared to the active metabolite 1,25-dihydroxyvitamin D (1,25VD) (4–6 hours). The best options for 25VD serum level evaluation methods are high performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS). There are reports, discussing the use of free 25VD as indicator of VD status. However, in renal disease,

the ratio between free and total 25VD remained unchained; therefore, total 25VD is the indicator of VD status in CKD [3].

Generally, 25VD level has reverse association with parathyroid hormone (PTH) levels. In addition, higher 25VD is associated with higher calcium intestinal reabsorption. However, at 25VD ≥ 75 nmol/l, no reduction in PTH levels and no increase in calcium intestinal reabsorption occurs [4, 5]. Therefore, 25VD ≥ 75 nmol/l is regarded as a cut-off value for vitamin D sufficiency.

No generally accepted definition for VD deficiency exists, as authors choose cut-off value either serum 25VD of 25 nmol/L [6] or serum 25VD of 50 nmol/L [7]. However, target levels of 75 nmol/L are recommended, taking into consideration the clinical importance of mild VD insufficiency (25VD between 50 and 74.9 nmol/L) [7, 8].

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health [one of the following: estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2,presence of proteinuria, structural abnormalities of the kidney detected on imaging, pathological findings detected on kidney biopsy, urine sediment pathology, electrolyte abnormalities due to tubular disorders, history of kidney transplantation] [9]. CKD patients are at increased risk for VD deficiency; therefore, they require VD screening [7].

3. Vitamin D metabolism in health and renal disease

3.1 VD metabolism in healthy subjects

VD is synthesized predominantly endogenously (approx. to 90% of the total VD in human body). In the skin, the ultraviolet light transforms 7-dehydroxycholesterol (provitamin D) to pre-vitamin D, which under the influence of body temperature spontaneously isomerizes to cholecalciferol (vitamin D3). Approximately, 10% of total body VD is taken orally (vitamin D2, ergocalciferol, and cholecalciferol). VD is transported via VD-binding protein to the liver, where it is hydroxylated to 25VD. The next step in VD activation is hydroxylation of 25VD by the enzyme 1α-hydroxylase (CYP27B1) to 1,25VD, which is the active VD metabolite. The process occurs predominantly in the renal tubules. In addition, non-renal CYP27B1 was detected in skin (basal keratinocytes and hair follicles), lymph nodes (granulomata), colon (epithelial cells and parasympathetic ganglia), pancreas (islets), adrenal medulla, brain (cerebellum and cerebral cortex), prostate epithelial cells, and placenta (decidual and trophoblastic cells) [10], indicating the wider significance of the VD metabolites. Finally, 1,25VD is inactivated by the enzyme 24-hydroxylaze.

1,25VD exerts its effect via the vitamin D receptor (VDR), which is detected in all human organs. 1,25VD binds to VDR, the complex forms a heterodimer with the receptor for retinoid X (RXR) within the nucleus. The 1,25VD-VDR-RXR complex binds to vitamin D reacting elements, modulating gene expression. The highest expression of VDR is detected in bones, small intestines, and parathyroid gland. VDR activation leads to influencing bone metabolism), increase of calcium and phosphate absorption, and PTH secretion suppression. However, due to the wider VDR distribution in human body, its activation is associated with effects beyond influencing calcium-phosphorus metabolism–renin-angiotensin system (RAS) suppression and cardiac hypertrophy prevention (myocardial VDR), diabetes mellitus control (pancreatic VDR), and immune system modulation (VDR in the immune cells).

The above-mentioned stages of VD metabolism form the so called VD axis.

3.2 VD metabolism in CKD

All levels of VD metabolism are significantly affected in renal disease.

Cholecalciferol synthesis is reduced in uremic skin. In addition, these patients are usually older, with reduced exposure to sunlight, which is additionally associated with poorer skin VD synthesis. What is more, oral VD intake is decreased due to protein intake reduction.

25VD is reduced in CKD due to reduced amount of its precursor, increased loss in nephrotic patients, and 25VD sequestration in adipose tissue due to higher rate of obesity in CKD patients [11, 12].

Even during the initial stages of CKD (eGFR below 60 ml/min/1.73 m^2) due to reduced phosphate tubular excretion, higher levels of fibroblast growth factor 23 (FGF-23) occur, which suppress CYP27B1 activity. Furthermore, phosphatemia and metabolic acidosis decrease enzyme activity too. In addition, 1,25VD levels in renal disease are reduced because of increased catabolism due to increased FGF-23 levels. Finally, the smaller number of functioning tubules is directly associated with lower 1,25VD production in advanced CKD.

VDR is affected in CKD too. Low 1,25VD downregulates of VDR expression [13]. In areas of nodular growth in the parathyroid gland reduced VDR content is detected. In uremia, there is significant decrease in VDR-RXR binding to vitamin D reacting elements, as well as reduced RXR content in the parathyroid glands, explaining increased PTH levels without the presence of hypocalcaemia and hyperphosphatemia [14]. Hypocalcaemia in advanced CKD increases the parathyroid levels of calreticulin, a cytosolic protein that binds the DNA-binding domain of nuclear receptors, thus blocking VDR-mediated transactivation. Higher levels of inflammatory cytokines were found to be associated with impaired binding of VDR-RXR to vitamin D

VD axis	Healthy subjects	In CKD
Cholecalciferol/ergocalciferol	Skin synthesis from UV light or oral intake	• Reduced skin synthesis (age, uremia, reduced UV exposure) • Reduced oral intake
25-hydroxyvitamin D(25VD)	Hepatic synthesis (25-hydroxylase)	• Reduced amount of its precursor • Increased loss in nephrotic patients • 25VD sequestration in adipose tissue
1,25-dihydroxyvitamin D(1,25VD)	Hydroxylation in renal tubules (1α-hydroxylase) and other organs	• Increased catabolism • Suppressed 1α-hydroxylase activity • Reduced synthesis in renal tubules in advanced CKD
Vitamin D receptor(VDR)	Widely spread in human body, esp. bone and parathyroid glands (calcium-phosphorus metabolism) In all other organs (pleiotropy)	• Downregulated expression (low 1,25VD, hypocalcaemia) • Impaired binding to VDRE (uremia, inflammatory cytokines, etc.) • Reduced VDR content in parathyroid glands (hypertrophy)

CKD, chronic kidney disease; VDRE, vitamin D reacting elements; UV, ultraviolet.

Table 1.
Vitamin D axis in health and in renal disease.

reacting elements, contributing to vitamin D resistance in patients on hemodialysis [15]. Finally, hypocalcaemia in CKD suppresses the calcium-sensing receptor (CaSR) in the parathyroid glands, which in turn downregulates parathyroid VDR expression; use of calcimimetics upregulated VDR expression in rat models [16].

The VD axis in health and renal disease is depicted in **Table 1**.

4. Vitamin D deficiency: clinical implications in renal disease

The major mechanisms for abnormal VD metabolism and VD deficiency were outlined in the section above. Of particular importance is hyperphosphatemia, caused by initial renal damage, leading to higher FGF-23 levels, which in turn suppresses CYP27B1 activity and increases 1,25VD catabolism. Suboptimal VD levels are the basis of the abnormal calcium-phosphate metabolism in renal disease. Currently, the term CKD-associated mineral bone disorder (CKD-MBD) is used to define the wide spectrum of CKD-related abnormalities in calcium-phosphate metabolism, as their importance spans beyond bone health.

4.1 CKD-associated mineral bone disorder (CKD-MBD)

CKD-MBD comprises of three major aspects—biochemical abnormalities, bone changes, and vascular calcifications [17].

4.1.1 Biochemical abnormalities in CKD-MBD

The biochemical abnormalities in CKD-MBD represent the laboratory aspect of the disorder. These include calcium level (ionized or total), phosphate level, PTH, alkaline phosphatase (total or bone specific), and VD status (25VD). Other indicators, such as 1,25VD and FGF-23 are not measured routinely. The earliest changes occur in PTH and VD metabolites—the abnormal values for PTH, 25VD and 1,25VD are detected in eGFR<60 ml/min/1.73 m^2, whereas abnormal calcium and phosphate levels are detected in eGFR below 40 and remain stable until eGFR<20 ml/min/1.73 m^2 [18].

According to the current guidelines, testing for calcium, phosphate, PTH, and alkaline phosphatase should be initiated in eGFR<60 ml/min/1.73 m^2; the frequency of laboratory evaluation should be based on the rate of CKD progression, the magnitude of abnormalities, and the evaluation of treatment's effectivity. Similarly, 25VD should be tested in patients with eGFR<60 ml/min/1.73 m^2 and frequency of testing depends on baseline values and therapeutic interventions [17]. The timing and frequency suggested by Kidney Disease: Improving Global Outcomes (KDIGO) are summarized in **Table 2**.

4.1.2 Bone disorders in CKD-MBD

Bone involvement in CKD [renal osteodystrophy (ROD)] is of pivotal importance, as it is associated with bone fractures (asymptomatic or symptomatic), bleeding, chronic disability, poorer life quality, and higher mortality in renal disease. In children with CKD, it leads to growth retardation and skeletal deformities [17].

Several types of bone histological changes can be detected in CKD, according to three major histological indicators: turnover, mineralization, and volume. Bone turnover (T) is a parameter, corresponding to bone formation rate. It can be abnormally low, normal, or very high and is best assessed via bone biopsy and tetracycline

Indicator	CKD stage 3	CKD stage 4	CKD stage 5 and on dialysis (CKD 5D)
Calcium and phosphorus	6–12 months	3–6 months	1–3 months
PTH and alkaline phosphatase	Baseline	6–12 months	3–6 months
25-Hydroxyvitamin D	Baseline	Baseline	Baseline

CKD, chronic kidney disease; PTH, parathyroid hormone.

Table 2.
Suggested testing for biochemical indicators of CKD-MBD according to CKD stage.

labeling. Mineralization (M) is the second parameter. Normally, the osteoblasts lay down new collagen and direct mineralization of the matrix. This process is impaired in CKD, leading to thickened osteoid. Mineralization is measured by osteoid maturation time and mineralization lag time. The osteoid maturation time is the osteoid width divided by the distance between labels per day. The mineralization lag time is the osteoid maturation time adjusted for the percentage of osteoid surface that has a tetracycline label. Mineralization is classified as normal and abnormal. Bone volume (V) sums up bone formation and resorption rates. It is generally accepted that bone volume is expressed as bone volume per tissue volume and is classified as low, normal, and high bone volume.

According to the TMV classification of bone histology in CKD, the following ROD categories are recognized [19]:

1. Adynamic bone disease (AD)—low-turnover bone disease with normal mineralization. Volume can be low, but in some patients with normal mineralization and low turnover, it will be normal. AD is usually associated with PTH oversuppression, including overdose of VD analogs or calcitriol

2. Mild secondary hyperparathyroidism related bone disease (MHPTBD)—medium-to high bone turnover, any bone volume, normal mineralization

3. Osteitis fibrosa (OF)—represents a more advanced form of high-turnover disease, compared to MHPT, any bone volume and normal mineralization

4. Osteomalacia (OM)—low-turnover bone with abnormal mineralization. The bone volume may be low to medium, depending on the severity and duration of the process and other factors that affect bone health

5. Mixed uremic osteodystrophy (MUO)—represents features of the above mentioned variants; for example, a combination of high-turnover, normal bone volume, with abnormal mineralization

In addition, age related/postmenopausal osteoporosis can be detected. Measurement of bone mineral density [by using dual-energy X-ray absorptiometry (DXA)] is most informative in CKD stages 1–2; in these cases, low BMD is associated with osteoporosis and treatment is performed as in the general population. Patients with low BMD and CKD stages 3–5 are designated as having CKD-MBD with low BMD. Recent reports demonstrate that BMD testing can predict fracture risk in eGFR<60 ml/min/1.73 m^2. The current KDIGO guidelines broaden the indications for BMD testing in CKD stages 3–5D to assess fracture risk, if it will have effect on treatment. Finally, normal histology is also possible [17, 20].

Clinical presentation	HTMBD	LTMBD
	Arthralgia	Arthralgia
	Bone pain	Bone pain
	Calciphylaxis	Calciphylaxis
	Bone fractures	Bone fractures
	Muscle weakness, spasms, tetany, paresthesia, convulsions (hypocalcaemia)	Aluminum toxicity—anemia, dementia
	Vomiting, nausea, hypertension (hypercalcemia)	Vomiting, nausea, hypertension (hypercalcemia)
	Pruritus	Pruritus
	Myalgia	
Laboratory	**HTMBD**	**LTMBD**
Serum calcium	N in early stages ↓/N/↑ in advanced HTMBD	Early stages N/↑ Advanced stages—↑↑
Serum phosphate	N in early stages N to very high in advanced stages	Early stages N/↓ Advanced—↓/↑
BAP	N in early stages ↑ in advanced HTMBD	Early stages N/↓ Advanced—↓
PTH	N/↑ in early stages ↑↑↑ in advanced HTMBD	Early stages N/↓ Advanced stages ↓
Radiology	**HTMBD**	**LTMBD**
	Subperiosteal erosions—hands, clavicles, and pelvis	Fractures
	Vertebral osteosclerosis	Looser zones
	Brown tumors	Bone deformities
	Extraskeletal calcifications	Osteopenia and osteoporosis
Histology	HTMBD	LTMBD
	OF, MHPTBD	AD, OM

PTH, parathyroid hormone; BAP, bone specific alkaline phosphatase; N, normal; ↓, decreased; ↑, increased values; OF, osteitis fibrosa; MHPTBD, mild secondary hyperparathyroidism related bone disease; AD, adynamic bone disease; OM, osteomalacia.

Table 3.
Clinical presentation, laboratory, radiologic and histologic findings in low turnover mineral bone disease (LTMBD) and high turnover mineral bone disease (HTMBD).

It should be noted that histological findings differ according to renal replacement type. In patients on hemodialysis OF and MUO are the most common findings, in peritoneal dialysis–AD is detected in up to 50%, whereas in patients in CKD stages 3–5 not on dialysis the most common findings are OF and MUO. However, in the latter group, the highest percentage of normal histology is detected [20].

Bone biopsy is regarded as the golden standard for the precise diagnosis of the bone changes in CKD-MBD. Indications for bone biopsy are bone fractures, bone pain, unexplained hypercalcemia/hypophosphatemia, evaluation of the type of bone turnover (which may lead to treatment correction), and suspected aluminum toxicity. Planning antiresorptive treatment in eGFR<30 ml/min/1.73 m^2 is currently not an indication for bone biopsy, as no evidence exists, linking bisphosphonate use to higher AD prevalence in CKD [17]. The most widely recognized disadvantages

of the procedure are pain, laborious procedure, time-consuming, and expensive histological evaluation, as well as insufficient histopathological expertise [21].

These limitations restrict the wide use of bone biopsy. Therefore, markedly elevated PTH and bone-specific alkaline phosphatase can be used in clinical practice to predict bone turnover in CKD-MBD. Thus, two types of mineral bone diseases are defined—high turnover mineral bone disease (HTMBD) and low turnover mineral bone disease (LTMBD). In cases, in which clinical and laboratory data are inconclusive of the type of bone turnover, bone biopsy should be considered [17]. The clinical, laboratory, radiological, and histological characteristics of the both entities are summarized in **Table 3**.

4.1.3 Vascular calcification in CKD-MBD

Vascular calcification (VC) is deposition of calcium phosphate in vascular tissues. It presents with calcification of arterial media, intima, valves, and rarely with calcific uremic arteriolopathy (calciphylaxis). Normally, this occurs with aging. However, the process is accelerated in CKD and leads to increased mortality and morbidity. Initially, it was regarded as a finding in patients with end-stage renal disease (ESRD), but currently, it is detected in early CKD stages in adults and in children with ESRD, thus depicting a more complicated picture [22].

Patients with VC are regarded as having the highest risk for cardiovascular events. The diagnosis is based on abdominal lateral radiograph (vascular calcifications), echocardiogram (valvular calcifications), or computer tomography [17].

The association of VC with VD status in CKD is not well defined as contradicting reports exist. Two report demonstrate, that lower serum 1,25VD is associated with increased risk for and demonstrated that 25VD has no association with VC [23, 24]. As arterial stiffening is regarded as related pathology to VC in CKD, it should be noted that two recent interventional studies demonstrated improvement of endothelial dysfunction in CKD patients after cholecalciferol supplementation [25–27]. Higher serum levels of 1,25VD and high doses of VD supplementation increased the risk for VC [23, 28], thus indicating the dual role of VD in vascular health.

Finally, the type of VD treatment may be important too. Generally, vitamin D analogs (VDA) demonstrate similar effectivity in reduction of PTH levels to calcitriol, with lower toxicity—lower rates of hypercalcemia and hyperphosphatemia, thus suggesting lower risk for supplementation-enhanced VC. Unfortunately, more trails are needed to evaluate the effect of different supplementation types on VC prevalence. In addition, new VDA are being evaluated in the treatment of CKD-MBD, with more expressed cardiac protection and less hypercalcemia and hyperphosphatemia than paricalcitol [29–31].

4.2 VD pleiotropy in renal disease

As mentioned above, the VDR and the enzyme CYP27B1 have wider distribution in the body and are being expressed in organs not involved in calcium-phosphate metabolism. This indicates a greater physiological importance of the VD axis, spanning beyond skeletal physiology. These extraskeletal properties are designated as pleiotropic effects of VD. In this sub-section, the current knowledge of VD pleiotropy in CKD patients will be presented.

4.2.1 VD pleiotropy in CKD: proteinuria and CKD progression

Poorer VD status was associated with higher proteinuria and faster progression of CKD. In addition, VDR activation was found to slow CKD progression in immune and non-immune renal diseases.

In IgA nephropathy, human studies associated poorer VD status with poorer clinical outcomes [32]. In addition, calcitriol supplementation suppressed proteinuria in IgA patients by activating the VDR and thus influencing cytokine and leukotriene metabolism [33].

Recent studies demonstrated the importance of VD axis in systemic lupus erythematosus (SLE) and lupus nephritis (LN). Poorer VD status correlated with higher SLE activity, whereas poorer VDR expression in renal tissue was linked to higher renal activity and more severe renal lesions in patients with LN [34, 35]. Podocyte autophagy is a key factor in renal involvement in LN. A recent study showed that poorer VD status correlated with higher podocyte autophagy activity and VD effectively suppressed it in LN, thus protecting podocytes from antibody-mediated injury [36]. VD and VDR affect autophagy via different mechanisms: activating calcium-dependent intracellular kinases, downregulating mTOR expression, or upregulation of the cyclin-dependent kinase inhibitor *p19INK4D* [37].

However, VD has renoprotective effect in non-immune glomerular diseases too. In diabetic nephropathy (DN), both animal models and clinical trials demonstrate the negative correlation between low VD and the risk for DN and DN progression, as well as the beneficial effect of VD/VD analogs in reducing albuminuria, renal fibrosis, thus retarding disease progression [38, 39]. The effect can be explained with RAS suppression, suppression of inflammatory mediators [nuclear factor-kappa B (NF-κB), transforming growth factor-β(TGF-β)], suppressing the Wnt/β-catenin pathway, which is involved in epithelial to mesenchymal cell transition (EMT) in high glucose milieu, as well as upregulation of nephrin expression [39–41].

The mechanisms mentioned in DN (suppression of RAS, inflammation, EMT) are the basis of renal protection of VD in other renal diseases–in animal models and human clinical trials [33]. Additionally, an inverse correlation between VD status and proteinuria and blood pressure control in autosomal polycystic kidney disease (ADPKD) was reported, as well as reduction of proteinuria and hypertension on treatment with VDR agonist in experimental PKD. However, the findings are to be evaluated prospectively in interventional study in patients with ADPKD [42].

4.2.2 VD pleiotropy in CKD: autoimmunity, inflammation, and infection

The presence of VDR and CYP27B1 has been well recognized in the immune cells, which modulate their differentiation and proliferation. VD suppresses B-cell proliferation, modulates T-helper proliferation, favoring the T-helper type 2 subtype, thus suppressing inflammatory cytokine synthesis (IL17, IL21) and stimulating the production of anti-inflammatory ones (IL10). In addition, VD enhances the production of cathelicidin and β-defensin 2, as well as influences autophagy and apoptosis [33, 43]. All these properties of VD and VDR demonstrate the importance of VD axis in protective and pathological immunity.

4.2.2.1 VD and autoimmunity/inflammation

The role of VD in LN has been already discussed. Other studies, evaluating the VD–SLE association demonstrate that poorer VD is related to higher SLE activity in adults and children [44]. Different supplementation regimens also demonstrated improvement in inflammatory markers, disease activity indices, decrease in T-helpers types 1 and 17 [44]. However, despite the different papers, reporting beneficial effect from VD, a recent study demonstrated increase of SLE activity after exposing patients to UV radiation, despite improvement in VD status [45]. Thus, the SLE-VD correlation still remains to be clarified.

The rheumatoid arthritis (RA) and the inflammatory bowel disease (IBD) are diseases that influence kidney health by causing AA amyloidosis, which in turn progresses to ESRD. VD status was inversely associated with RA disease activity and RA-associated complications [46]. However, despite some reports, indicating beneficial effect of VD supplementation on T-helper 17 function, the results for VD supplementation currently are inconsistent [46, 47].

Several studies demonstrated lower VD status in patients with more aggressive IBD. However, the findings may be attributed to lower absorption of VD due to the active intestinal inflammation, especially in Crohn's disease [48, 49]. Interventional studies also demonstrated the beneficial effect of VD supplementation in suppressing pro-inflammatory markers in IBD. Yet, the importance of VD in IBD remains to be clarified [50, 51].

4.2.2.2 VD and infection

Infection is a well-recognized leading cause for death in CKD patients, especially those on dialysis. It was already mentioned that the VD axis plays a role in immunity by enhancing cathelicidin production. In dialysis patients, low cathelicidin levels were detected, which were associated with higher risk for infection and also modest correlation to 1,25VD levels was discovered [52]. Interventional studies also demonstrated the decreased risk for infection in dialysis patients. VD supplementation reduced significantly the risk for hospitalization due to acute respiratory infections in hemodialysis (HD) patients; in another study, VD supplementation decreased the risk for peritonitis in patients on peritoneal dialysis (PD) [53, 54]. A more recent study also demonstrated decrease in infection rates in dialysis patients treated with VDR analogs [55]. In contrast to these findings, Yildirim et al. failed to demonstrate a significant relation between VD status and inflammatory markers in CKD patients [56].

4.2.3 VD pleiotropy in CKD: neoplasia

An already mentioned paper demonstrated reduced malignancy-associated mortality in VDA-treated dialysis patients. However, the study did not evaluate the specific localization of the neoplasia, nor its histology [55]. Therefore, in this subsection, the most common malignant diseases will be reviewed and their association with VD. Unfortunately, the exact association between VD and neoplasia in CKD patients is not well evaluated, as CKD patients are usually excluded from large trials and registries [57].

4.2.3.1 Breast cancer

The reports evaluating the association between VD deficiency and breast cancer are inconsistent. The inverse association between breast cancer and VD, detected in several studies was not supported by more recent prospective studies. In addition, a controversy exists about the beneficial effect of VD supplementation on breast cancer risk and survival [44]. Unfortunately, the cited studies did not demonstrate data for CKD patients.

4.2.3.2 Colorectal cancer

Several studies demonstrate an inverse correlation between colorectal cancer and 25VD levels [58, 59]. The findings do not correspond to the results of a larger

study, detecting no significant association between colorectal cancer and VD status [60]. Unfortunately, the data from interventional trails with VD supplementation also have conflicting result for the effect of VD on colorectal cancer prevention and survival improvement [44, 61]. Similarly to breast cancer, the data for the association between colorectal cancer and VD status in renal patients is limited.

4.2.3.3 Other neoplasms

The results about the influence of VD on the risk for other malignancies are controversial. A large study (n = 70,563) evaluated the association of 25VD levels on the risk for prostate cancer, breast cancer, lung cancer, pancreatic cancer, colorectal cancer, ovarian cancer, and neuroblastoma. 25VD concentrations did not correspond to the risk for any of the mentioned neoplasias. Therefore, the authors do not support the regular VD screening as an attempt for cancer prevention [62]. In addition, a large multicenter study in patients on hemodialysis also did not demonstrate significant association between total cancer prevalence and VD deficiency [63].

Multiple myeloma (MM) is a plasma cell disease that often presents with kidney manifestations. Several studies reported high rates of VD deficiency in MM patients and specific alleles for VDR were associated with higher risk for MM [64, 65]. Lauter and Schmidt-Wolf established that lower VD levels were associated with more expressed plasma cell infiltration of the bone marrow. In this study, VD supplementation improved anemia, led to higher white blood cell and lower platelet count [66]. Yet, the risk for hypercalcemia should be taken into consideration when VD supplementation is applied in MM patients.

4.2.4 VD pleiotropy in CKD: diabetes mellitus, cardiovascular disease (CVD)

4.2.4.1 VD and diabetes mellitus

Basic science studies demonstrated improvement in glucose metabolism due to immunomodulatory effect (especially in diabetes type 1), improvement of β cell function by increase in insulin secretion, and decreasing insulin resistance by stimulating insulin receptor expression via activating the VDR. Other mechanisms such as RAS suppression and anti-inflammatory effect of VD were also taken into consideration. However, observational studies do not establish clear relationship between VD status and DM prevalence, as some studies support the association, whereas others do not [44]. Interventional trials also have conflicting results. Two recent prospective studies showed improvement in glucose metabolism after vitamin D supplementation was applied [67, 68]. Unfortunately, the studies did not evaluate patients with renal disease. Two interventional studies with paricalcitol failed to detect improvement in insulin resistance in patients CKD stages 3 and 4 and in dialysis [69, 70].

4.2.4.2 VD and cardiovascular disease (CVD)

CVD is a leading cause for mortality in CKD. As VDR and 27CYPB1 are expressed in the cells of the cardiovascular system, it could be expected that the VD axis can play a beneficial role in cardio-vascular health. A possible cardioprotection can be explained with RAS suppression and anti-inflammatory effects; VDR activation can improve cardiac muscle cells contractility and modulate their proliferation and growth. In addition, VD can improve peripheral vascular health by affecting endothelial and smooth muscular cells too [71].

Even though the association between VD deficiency and CVD has been recognized in the general population and in CKD, large randomized interventional studies failed to demonstrate improvement from VD supplementation in cardiovascular outcomes, cardiac structure, or function in CKD patients [72]. An improvement in blood pressure control and endothelial function (as measured by brachial artery flow-mediated dilatation) was observed after VD supplementation in the general population; however, in CKD patients, no significant antihypertensive effect was detected [73]. Similarly, the results for the effect on VD supplementation on arterial stiffness and endothelial function are conflicting [72, 73]. Therefore, the use of VD in renal disease in order to improve cardiovascular events is currently not recommended [72].

4.2.5 VD pleiotropy in CKD: muscle health, cognitive function, peritoneal fibrosis, and anemia

4.2.5.1 Muscle health and cognitive function

In hemodialysis (HD) patients, a positive relationship between muscle strength and VD levels was detected, with optimal handgrip strength in 25VD above 30 ng/ml (75 nmol/L). In ESRD patients, suboptimal VD was associated with lower quadriceps mass and increased risk for falls [74]. In addition, in PD patients, low 25VD was found to be the independent factor for global cognitive impairment due to the antioxidant and neuroprotective role of 1,25VD. This is of crucial importance, as PD is a home-based renal replacement therapy that needs adequate cognition and self-monitoring [75].

4.2.5.2 Anemia and peritoneal fibrosis

Treatment with VDA led to the improvement of anemia in ESRD patients. A possible mechanism is suppression of inflammation and direct stimulation of erythropoiesis. In addition, paricalcitol reduced PD-associated thickening of the peritoneum and prevented peritoneal fibrosis in animal models. However, recent study in PD patients did not detect any benefit from paricalcitol supplementation in preventing peritoneal remodeling. In contrast to these results, Kerschbaum et al. demonstrated protective effect of oral active VD against peritonitis in PD patients [33, 54, 76].

5. Vitamin D deficiency after kidney transplantation

Suboptimal 25VD is a commonly detected problem after kidney transplantation (KT) with prevalence above 80% of the kidney transplant recipients (KTRs). As KTRs are CKD patients, all mentioned factors, predisposing to impaired VD metabolism are valid for this cohort of patients, especially considering the fact that more than 50% of the KTRs have GFR<60 ml/min/1.73 m^2. In addition, transplant-specific factors influence VD synthesis: sun exposure avoidance due to the increased risk for skin malignancies, use of sun-protecting cosmetics (limiting further UV exposure), proteinuria after KT (increased loss in urine), higher prevalence of obesity after KT (reduced bioavailability), the presence of new onset diabetes after transplantation (NODAT) (by reducing intestinal absorption), use of steroids (increased 1,25VD catabolism), and calcineurin inhibitors (impaired 25VD liver synthesis) [77, 78]. Similarly to CKD in native kidneys, the VD-associated clinical implications after KT are categorized as post-transplant mineral bone disorder (PTMBD) and VD pleiotropy.

5.1 Post-transplant mineral bone disorder

Similarly to native kidneys, PTMBD consists of three aspects—biochemical abnormalities, bone involvement, vascular pathology and is associated with higher risk for fractures and death.

5.1.1 PTMBD: biochemical abnormalities

Significant changes occur in the biochemical indicators of calcium-phosphorus metabolism after KT. In the early post-transplant period, the fluctuations in the parameters are more pronounced as the graft function is rapidly changing. Due to the presence of functioning renal tubules and still high levels of PTH and FGF-23, hypophosphatemia and mild hypercalcemia are common. These changes usually normalize within months after KT as graft function stabilizes. Therefore, the current KDIGO guidelines recommend at least weekly testing for calcium and phosphorus immediately after KT [17]. FGF-23 and PTH rapidly decrease; however, PTH may be significantly elevated years after successful KT due to parathyroid cell hypertrophy. VD levels are low in the early post-transplant period; yet, suboptimal levels are very common later after KT [78].

In the late post-transplant period, current guidelines recommend the testing for calcium, phosphorus, PTH, and alkaline phosphatase to be performed according to the magnitude of the abnormalities, rate of progression of post-transplant CKD, and the presence of medical treatment. Practically, the timing is similar to patients with CKD stage 3–5 with native kidneys (see **Table** 2). 25VD should be tested at baseline and repeated testing should be performed according to the initial level and the presence of medical interventions. In our center, 25VD levels are monitored twice annually, taking into consideration its seasonal variations in the general population. Thus, a significant deterioration of VD status in the winter/fall was detected, allowing adequate seasonal supplementation to be initiated.

5.1.2 PTMBD: bone disease

Post-transplant bone disease is commonly observed after KT and encompasses ROD, osteoporosis, bone fractures, and osteonecrosis. Deterioration in BMD occurs mainly during the first 12 months, though BMD loss persists at lower rates after the first post-transplant year. The etiology is multifactorial: pre-existing CKD-MBD, duration of dialysis and transplantation, poor graft function, hypogonadism, higher rates of diabetes after KT, suboptimal VD levels, and use of immunosuppressive agents. Of these, steroids are of particular importance as their cumulative and mean dose is associated with decreased bone formation and bone density. Some reports indicate that calcineurin inhibitors can rise PTH levels and increase the risk of osteoporosis, but the findings are not uniformly accepted [17, 79].

In KTRs, not only fracture prevalence is significantly increased compared to the general population, but also fracture-associated complications, including mortality, are more common in the post-transplant setting. Major fracture sites are the hip (usually osteoporosis-associated) and the ankle/foot (atypical for osteoporosis), which demonstrate that both ROD and osteoporosis play an important role in bone fragility [80].

The use of DXA–BMD measurement is getting more attention in native CKD, as a growing body of evidence demonstrates that it can predict fracture risk across CKD categories. To date, only one retrospective study, total hip DXA measurement after KT was associated with increased fracture risk. In addition, a recent prospective study had similar findings [81, 82]. Despite the insufficient evidence for KTRs,

KDIGO suggests the use of BMD testing in all stages of post-transplant CKD in KTRs with high risk for osteoporosis, if the measurement will have effect on treatment. Bone biopsy can be considered to guide treatment [17].

5.1.3 PTMBD: vascular calcifications

VC is common after KT and is usually associated with pre-transplant uremia. In addition, most studies are semi-quantitative, thus making post-transplant VC progression assessment difficult. However, there are studies demonstrating a stop in progression or even improvement in VC in KTRs [83, 84]. Recognized risk factors for VC after KT are statin use, low 25VD levels, male sex, older age, and higher phosphate levels [85]. The data for the effect of immunosuppressive agents are conflicting. Mycophenolates proved to have protective effects against calcification, especially compared to steroids and calcineurin inhibitors; rapamycin suppressed smooth muscle cell proliferation, whereas everolimus impaired the vasoactive and antithrombotic function of the endothelium [86]. Therefore, more studies are needed in order to evaluate the effect of KT on VC.

5.2 VD pleiotropy after kidney transplantation

The graft survival at the tenth year after KT is significantly lower than the survival during the first 12 months. The explanation for these unsatisfactory results is poorer patient survival due to neoplasia, CVD, NODAT, calcineurin toxicity. It could be hypothesized that VD can improve graft and patient survival due to its pleiotropy. However, the trials in KTRs are small in number and in size, thus further research in this sphere is warranted.

5.2.1 VD pleiotropy after KT: proteinuria and renal protection

Observational studies linked poor VD status to poorer graft outcomes [86]. Our results also demonstrated that higher VD is associated with lower post-transplant proteinuria [87]. However, interventional studies did not fully support the VD–graft function association. Cholecalciferol supplementation failed to demonstrate renoprotection in prospective study [88]. However, in a recent prospective placebo-controlled study, paricalcitol ameliorated proteinuria in KTRs [89].

5.2.2 VD pleiotropy after KT: rejection

Observational studies demonstrated higher rates of acute rejection in VD deficient KTRs [90]. Unfortunately, interventional studies did not find protective role of cholecalciferol supplementation on rejection prevalence [88]. Therefore, the role of VD in rejection prevention after KT is not fully understood and is under debate.

5.2.3 VD pleiotropy after KT: infection

Infection is a major cause for death after KT. Several recent reports established negative correlation between VD status and infection risk, especially for cytomegalovirus and BK virus infections in KTRs [91, 92]. However, our observational study showed no association between VD status and prevalence of urinary tract infections after KT [93]. Furthermore, the VITA-D study did not establish positive effect of cholecalciferol supplementation on infection risk [88]. A probable explanation for the discrepancies in the studies are the different types of infection evaluated (e.g. in the VITA-D study the total infection risk was assessed). Probably, a more specific

approach should be chosen and the infection risk for specific etiological agent and its association to VD should be analyzed.

5.2.4 VD pleiotropy after KT: malignancies

Despite the anti-neoplastic properties of VD *in vitro* and in animal models, the evidence for anti-malignancy effect of VD in CKD patients and KTRs is insufficient. Observational studies report conflicting results for the association between post-transplant malignancies and VD status [86]. A recent study in our transplant center showed that VD-deficient KTRs had higher prevalence of non-cutaneous cancers [94]. A single center study established beneficial effect from active VD supplementation on post-transplant neoplasia rates [95]. The larger prospective, multicenter, double-blind, randomized, controlled study VITALE is currently being performed, which will evaluate the effect of cholecalciferol supplementation on malignancy risk after KT [96].

5.2.5 VD pleiotropy after KT: NODAT

The major risk factors for NODAT are use of steroids and calcineurin inhibitors. The data for VD-NODAT association are insufficient. The trial VITALE is to assess the effect of high and low doses cholecalciferol in VD–insufficient KTRs on NODAT prevalence [96].

5.2.6 VD pleiotropy after KT: cardiovascular disease

Marchal et al. established a significant association between lower 25VD and vascular calcification after KT [85]. However, a more recent study did not find a relationship between VD status and post-transplant hypertension and major CV events [97]. One of the aims of the already mentioned trial VITALE is to assess the effect of cholecalciferol supplementation on blood pressure control and CVD rates in KTRs [96].

6. Treatment of vitamin D deficiency in renal disease

6.1 Treatment with cholecalciferol, ergocalciferol, calcitriol, VDA

Supplementation with cholecalciferol (vitamin D3), ergocalciferol (vitamin D2), or treatment with the active vitamin D calcitriol or VDA suppresses PTH in secondary hyperparathyroidism in CKD. As a first step, a correction of hypocalcemia, hyperphosphatemia, and suboptimal 25VD levels should be performed. In more advanced CKD-related secondary hyperparathyroidism calcitriol and VDA can be initiated. It should be noted that over-suppression of the parathyroid gland due to overdose of the VD treatment is a major cause for AD. Therefore PTH, as well as serum phosphate and calcium, should be regularly monitored. It should be noted that the optimal PTH values for dialysis patients are two times up to nine times the upper normal limit, whereas for patients not on dialysis the optimal range is not established. If trend for lowering/rising values is present, changes in treatment should be changed so that the negative trends be reverted [17]. Similarly, in KTRs cholecalciferol/calcitriol/VDA treatment should also take these trends into consideration.

6.1.1 Supplementation with cholecalciferol/ergocalciferol

In the general adult population, supplementation doses of VD at least 600 IU daily; however, if improvement in VD status is needed, doses of at least

1500–2000 IU per day should be prescribed. The maximal dose VD without medical supervision should be 4000 IU daily. Cholecalciferol and ergocalciferol are equally effective [98]. The KDIGO guidelines recommend VD deficiency in CKD patients and in KTRs to be treated as in the general population. It is the initial therapeutic step, together with correction of hypocalcemia and hyperphosphatemia, as it effectively suppresses PTH in CKD stages 3–5 not on dialysis. More aggressive approach is to be avoided as modest PTH elevation is regarded as adaptive mechanism in declining GFR [17].

6.1.2 Treatment with calcitriol and VDA

Calcitriol is naturally existing 1,25VD, whereas VDA are synthetic derivatives of vitamin D2 (paricalcitol, doxercalciferol) and vitamin D3 (alfacalcidol, falecalcitriol, 22-oxacalcitriol). Despite the existing trials demonstrating positive effect of calcitriol/VDA on biochemical abnormalities, more recent studies do not demonstrate improvement in patient-centered end-points, such as left ventricular mass index and heart function; however, hypercalcemia was observed. Taking into account that modest PTH elevation is a possible adaptive response in CKD, the lack of significant clinical effects and higher risk for hypercalcemia, the use of calcitriol and VDA is not routinely recommended in CKD stages 3–5 not on dialysis. Their use is advocated in cases of severe and progressive secondary hyperparathyroidism and eGFR below 30 ml/min/1.73 m^2 or dialysis patients [17].

The data for hypercalcemia rates in calcitriol and VDA are conflicting. Zand et al. demonstrated lower hypercalcemia prevalence in patients treated with paricalcitol; other reports established no difference in hypercalcemia between calcitriol and paricalcitol [29, 99].

6.1.3 Other therapeutic measures

Other measures, recommended by KDIGO that optimize VD treatment in CKD-MBD are avoidance of hypercalcemia, reduction of phosphate serum levels, including phosphate dietary restriction, limitation of the use of calcium-based phosphate binders, calcium dialysate concentrations within the range of 1.25 and 1.50 mmol/l [17].

6.1.4 Novel agents

6.1.4.1 Calcifediol

Calcifediol is an oral 25-hydroxyvitamin D3. A study demonstrated reduction in PTH levels without changes in phosphate, calcium, and FGF-23 levels in CKD patients. In this chapter, patient-related outcomes were not assessed [100]. Further trials are needed to clarify the use of calcifediol in renal disease.

6.1.4.2 Vitamin K

Vitamin K plays a crucial role in vascular health. It serves as a cofactor for γ-glutamyl carboxylation, which converts glutamate into γ-carboxyglutamate (Gla). In vitamin K insufficiency, which is common in CKD, higher levels of desphosphorylated-uncarboxylated matrix Gla-protein (MGP) are established, which are associated with VC, as MGP serves as calcification inhibitor. Vitamin K supplementation increases MGP carboxylation. What is more, VD supplementation upregulates MGP synthesis, whereas vitamin K suppressed 1,25VD-associated calcinosis [101, 102].

Therefore, it can be hypothesized that vitamin K supplementation in CKD can be an adjuvant treatment to VD supplementation and will decrease its adverse effects. Further research of the efficacy and safety of vitamin K supplementation in CKD is needed.

7. Conclusion

VD deficiency in renal patients has been a burning issue in nephrology for many years. Yet, many questions remain unanswered. Of particular interest are the effect on VD treatment on clinical outcomes, especially death and cardiovascular events; VD-associated adverse events in CKD; VD pleiotropy in renal disease (randomized controlled prospective interventional studies are needed); the use of novel therapeutic agents should be further evaluated (vitamin K, new VDA, calcifediol). In addition, new biomarkers, evaluating bone health in CKD and new techniques, evaluating BMD and fracture risk may guide VD treatment more accurately. Therefore, new diagnostic and therapeutic strategies can be expected in the future.

Conflict of interest

The authors declare no conflict of interest.

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