Chapter 2

Vitamin D and Renal Disease

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Additional information is available at the end of the chapter

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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 1α 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].

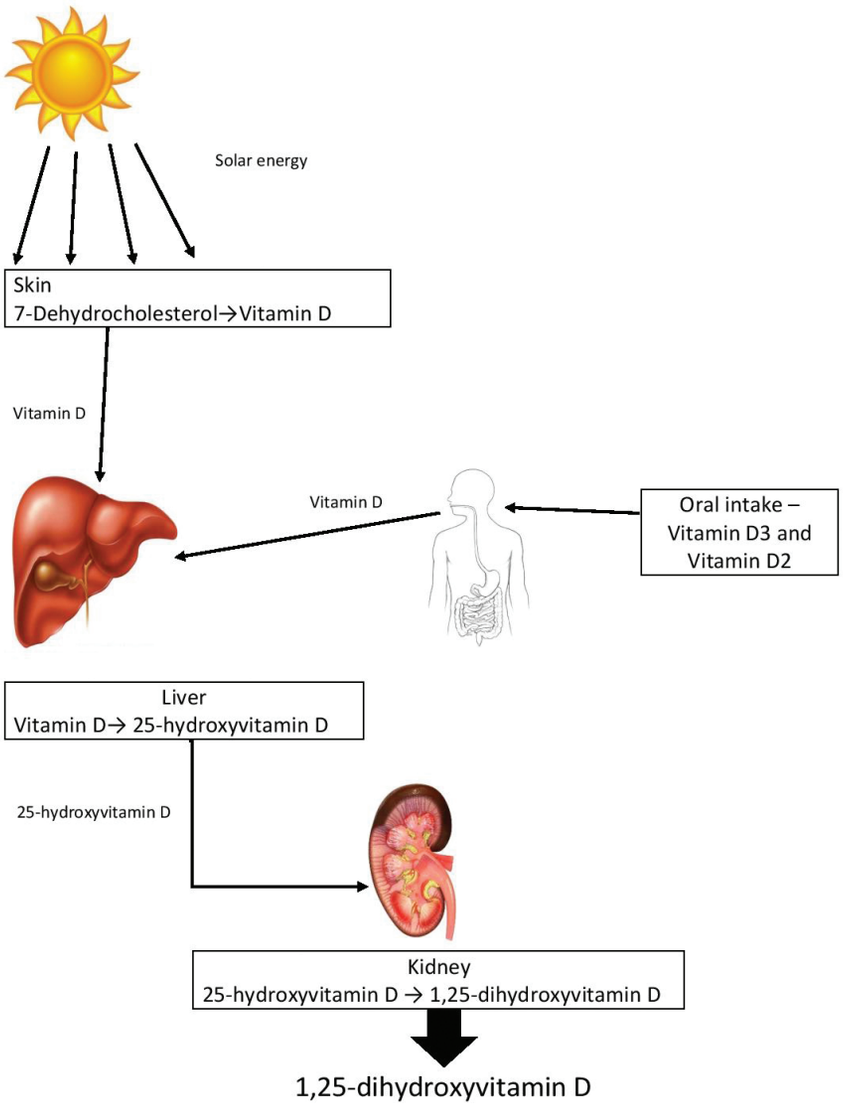

Figure 1. Vitamin D synthesis.

CYP27B1 activity is influenced by different factors. Parathyroid hormone (PTH), prolactin, human growth hormone, low serum calcium, and phosphorus increase CYP27B1 activity, whereas 1,25dihydroxyvitamin 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].

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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 phosphatonins, 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**.

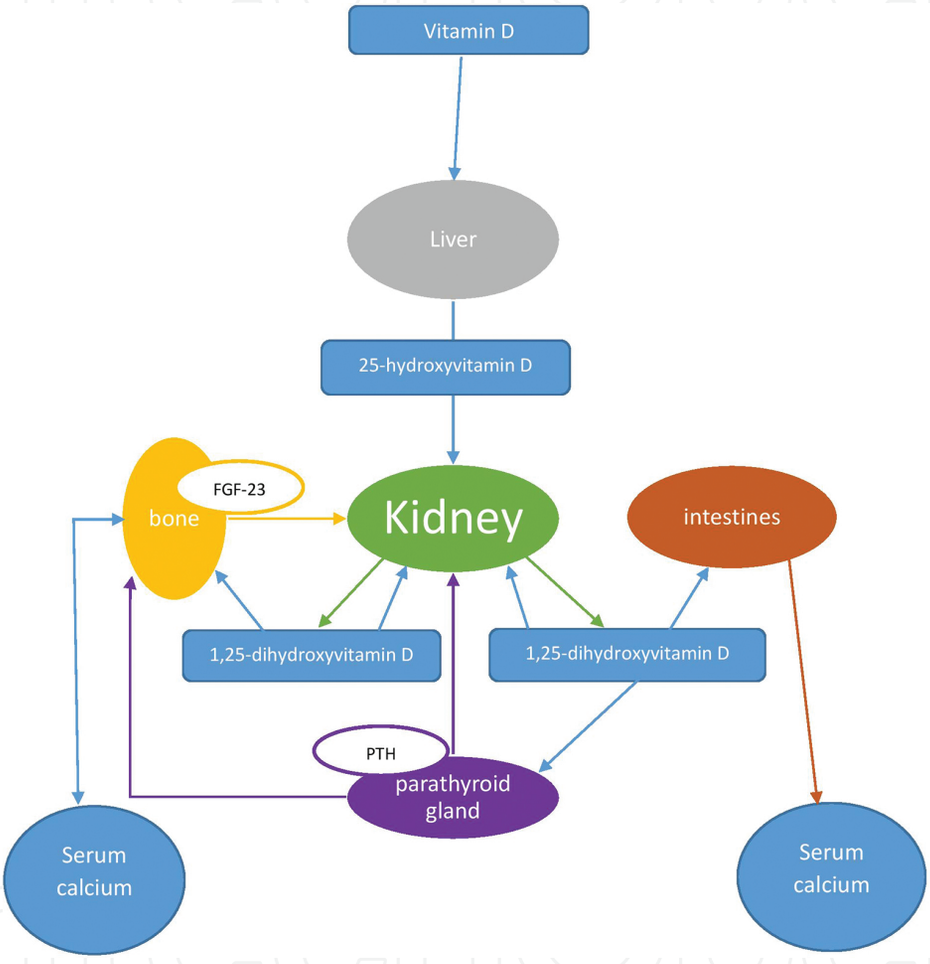

Figure 2. Role of the kidney in calcium-phosphorus metabolism.

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**).

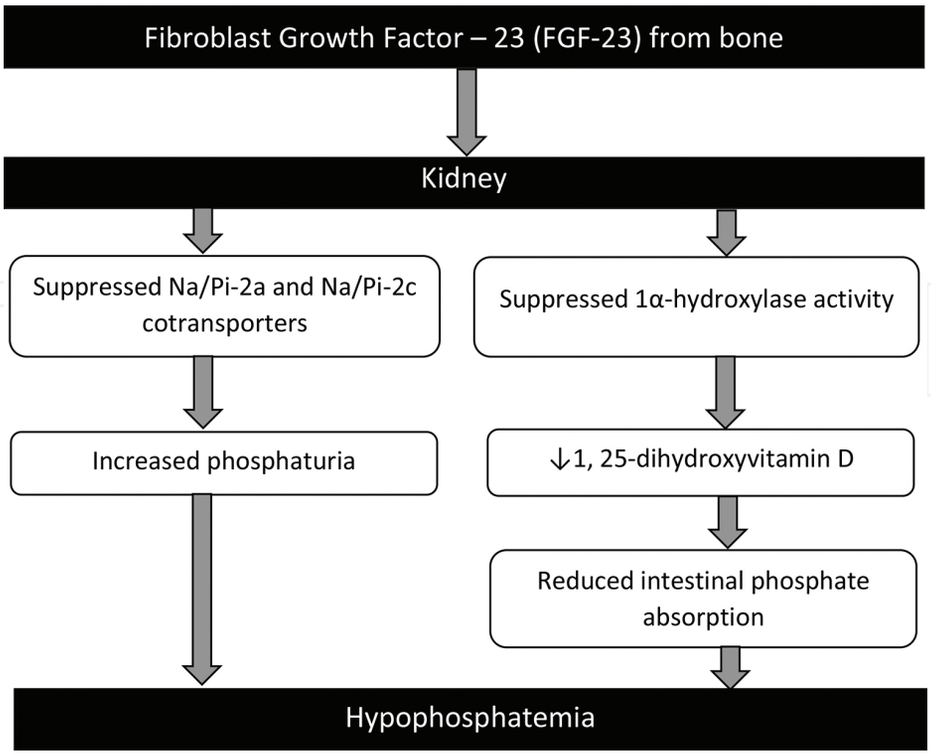

Figure 3. Role of FGF-23 in phosphate homeostasis.

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 m^2 (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 m^2, 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 ostheodystrophy, taking into consideration a broader problem in CKD patients [21].

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
- Vascular or other soft tissue calcification.

Definition of renal osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

Table 2. KDIGO classification of CKD-MBD and renal ostheodystrophy [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 m^2 [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 m^2, 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].

Factor	Mechanism
Advanced patient's age	Reduced skin synthesis of cholecalciferol
Dietary restrictions in CKD	Reduced oral intake
Uremia	Reduced skin synthesis of cholecalciferol
Proteinuria	Increased urine loss
Higher prevalence of African race in CKD	Reduced skin synthesis of cholecalciferol
Higher prevalence of obesity	Reduced bioavailability of 25VD

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-VDR-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

cellular membrane, thus placing the VDR-VD axis not only in the middle of genomic effects but also in activation of rapid transmembrane pathways [35].

In uremia, significant changes in VDR function occur. Low levels of 1,25VD lead to downregulation of VDR expression [36]. In addition, in areas of nodular growth in the parathyroid gland reduced VDR content was detected [37]. In CKD, there is a significant decrease in VDR-RXR binding to vitamin D reacting elements, as well as reduced RXR content in the parathyroid glands of uremic animal models, explaining increased PTH levels without the presence of hypocalcemia and hyperphosphatemia [38]. Hypocalcemia in advanced renal failure increases the parathyroid levels of calreticulin, a cytosolic protein that binds the DNA-binding domain of nuclear receptors, thus blocking VDR-mediated transactivation [39]. Higher levels of inflammatory cytokines were found to be associated with impaired binding of VDR-RXR to vitamin D reacting elements, contributing to vitamin D resistance in patients on hemodialysis [40]. Finally, hypocalcemia in CKD suppresses the calcium-sensing receptor (CaSR) in the parathyroid glands, which in turn downregulates parathyroid VDR expression. Stimulating CaSR by increasing extracellular calcium or by using calcimimetics upregulated VDR expression in rat models [41].

3. Vitamin D axis in renal disease: clinical implications

3.1. CKD-MBD: biochemical abnormalities

Monitoring biochemical indicators in CKD should start at CKD stage 3 (GFR below 60 ml/min). The most important indicators are serum calcium, phosphate, PTH, and alkaline phosphatase. 25VD should be tested too, with further testing should be considered according to initial levels and the need for supplementation. Generally, laboratory trends are more important than single values and monitoring should be tailored to CKD stage and presence of active treatment. The suggested KDIGO frequencies for monitoring calcium, phosphate, 25VD, and PTH are shown in **Table 4**.

Indicator	CKD stage 3	CKD stage 4	CKD stage 5 and 5D
Calcium and phosphate	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

Table 4. Suggested frequency for monitoring biochemical abnormalities in renal disease [19, 21].

3.2. CKD-related mineral bone disease (CKD-MBD)

As it has already been mentioned, pathological changes in VD metabolism are present in the early CKD stages. Thus, the majority of renal patients have CKD-related bone disease, significantly higher fracture risk and higher morbidity and mortality compared to the

general population are detected in patients with GFR < 60 ml/min/1.73 m^2. Bone pathology is one of the most extensively studied complications in CKD. Often CKD-related bone changes overlap with age-related and postmenopausal osteoporosis, making the picture even more complicated.

3.2.1. Bone histology in CKD

Bone histology in CKD represents a broad spectrum of pathological changes, which are classified according to bone turnover, mineralization, and bone volume (TMV classification) [42].

Bone turnover (T) is a parameter, corresponding to bone formation rate (BFR). BFR can be abnormally low, normal, or very high. BFR is best assessed via bone biopsy and tetracycline labeling. Other measurements that can be used for estimating BFR are osteoblastic surface, the number of active osteoblasts, and the osteoid surface, but none is as accurate as tetracycline testing [43].

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 [21, 43]. Mineralization is classified as normal and abnormal. A typical example of abnormal mineralization is osteomalacia (OM), where increased osteoid volume, increased osteoid maturation time, or increased mineralization lag time are detected.

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 ranges between low and high. There are different ways to measure bone volume—dual-energy X-ray absorptiometry (DEXA) and quantitative computed tomography (QCT). These two methods, however, have disadvantages in cases with low mineralization, as they reflect primarily bone density. In addition, there are differences in the microstructure in different diseases. In idiopathic osteoporosis, both cortical and cancellous bone volumes decrease, whereas in hemodialysis patients the cortical compartment is reduced, but the cancellous one is increased [44]. Bone volume is classified as low, normal, and high [42].

Evidently, the above-mentioned parameters are linked between each other and can be most accurately assessed via bone biopsy. The procedure, however, has its disadvantages. First, its invasive character is associated with pain, bleeding, and infection. The more serious problem is the representativeness of the obtained sample. Finally, few centers can use the bone-specific histomorphological staining techniques. Hence, though recommended by the KDIGO group, bone biopsy is not routinely performed in everyday renal practice. There are several indications for bone biopsy [42] (**Table 5**).

• inconsistencies among biochemical parameters
• unexplained skeletal fracture or bone pain
• severe progressive vascular calcification
• unexplained hypercalcemia and hypophosphatemia
• suspicion of overload or toxicity from aluminum
• before parathyroidectomy if there has been significant exposure to aluminum in the past or if the results of biochemical determinations are not consistent with advanced secondary or tertiary hyperparathyroidism
• before beginning treatment with bisphosphonates

Table 5. Suggested indications for bone biopsy.

Once the individual parameters for TMV are obtained, personal graph can be formed.

Osteomalacia is currently described as a 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. Adynamic bone disease (AD) is currently defined as low-turnover bone with normal mineralization. Bone volume can be at the lower end of the spectrum, but in some patients with normal mineralization and low turnover it will be normal. Mild HPT (mild hyperparathyroid-related bone disease) and osteitis fibrosa (or advanced hyperparathyroid-related bone disease) are currently used as distinct categories, but in actuality represent a range of abnormalities along a continuum of medium to high turnover, and any bone volume depending on the duration of the disease process. Mixed uremic osteodystrophy is variably defined internationally, but generally it represents with combination of the above-mentioned biopsy findings. For example, it can present as high-turnover, normal bone volume, with abnormal mineralization [42].

In summary, the TMV classification system more precisely describes the range of pathologic abnormalities that can occur in patients with CKD. However, due to the difficulties in performing bone biopsy, the older clinical classification is still used, based on bone turnover—high-turnover mineral bone disease (HTMBD) and low-turnover mineral bone disease (LTMBD). The KDIGO work group currently does not support the use of DEXA measurement of bone density and bone-derived turnover markers of collagen synthesis and breakdown in GFR below 60 ml/min/1.73 m^2 as these parameters do not predict the type of renal osteodystrophy. In contrast, in patients with CKD stages 3–5D, measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover [21].

3.2.2. High-turnover mineral bone disease (HTMBD)

The typical histological substrates of HTMBD are osteitis fibrosa and mild HPT-related bone disease. The prevalence of HTMBD has remained stable over the last years, ranging between 40 and 50% in CKD patients [45].

Generally, HTMBD is asymptomatic and is preceded by laboratory and X-ray changes. Clinical presentation is usually not typical and consists of nonspecific pain in the lower back, hips, and legs, aggravated by weight bearing. Bone fractures and bone deformities are also common. In addition, symptoms associated with impaired calcium levels (hypocalcemia or hypercalcemia) are present. Extraskeletal calcifications are commonly detected, as well as pruritus. Rarely calciphylaxis (calcific uremic arteriolopathy) is detected. Increased mortality is present.

Laboratory changes comprise of low calcium and high phosphate levels (in advanced CKD stages), elevated bone-specific alkaline phosphatase (BAP), and PTH. Calcium levels can be elevated due to calcium oral supplementation or vitamin D overdose. BAP and PTH are currently the most reliable noninvasive markers for bone turnover.

Routine radiology imaging is insensitive for the type of osteodystrophy and is performed only when symptoms appear. However, certain findings are described, which are not specific for CKD-related bone disease [46].

Table 6 summarizes the clinical, laboratory, and radiology findings in HTMBD.

Clinical presentation of HTMBD
Arthralgia
Bone pain
Myalgia
Bone fractures
Muscle weakness, spasms, tetany, paresthesia, convulsions (hypocalcemia)
Vomiting, nausea, hypertension (hypercalcemia)
Pruritus
Calciphylaxis
Laboratory findings
Serum calcium – N in early stages; ↓/N/↑ in advanced HTMBD
Serum phosphate – N in early stages, N to very high in advanced stages
BAP – N in early stages; ↑ in advanced HTMBD
PTH – N/↑ in early stages; ↑↑↑ in advanced HTMBD
Radiology findings
Subperiosteal erosions—hands, clavicles, and pelvis
Vertebral osteosclerosis
Brown tumors
Extraskeletal calcifications

Abbreviations: BAP, bone-specific alkaline phosphatase; PTH, parathyroid hormone; N, normal; ↓, decreased; ↑, increased values.

Table 6. Clinical presentation and laboratory/radiology findings in high turnover mineral bone disease (HTMBD).

3.2.3. Low-turnover mineral bone disease (LTMBD)

LTMBD encompasses two entities in bone pathomorphology in CKD—osteomalacia and adynamic bone disease. Osteomalacia presents with low turnover and abnormal mineralization, increased osteoid matrix, and is more frequently associated with aluminum toxicity. AD is characterized with low turnover and bone acellularity. In AD even the matrix formation is reduced, thus the mineralization seems unchanged [21]. OM in CKD prevalence is decreasing significantly since 1995 and currently is bordering at 0%. However, AD is getting more common than all other subtypes of renal osteodystrophy, with prevalence peaking to 40% [44].

AD increases in importance not only due to its higher incidence, but also because of its clinical role in CKD. AD is associated with cardiovascular calcification, increased mortality, and higher fracture risk compared to HTMBD [46]. The major factors contributing for AD development are increased use of calcium-containing phosphate binders, excessive use of calcitriol/vitamin D analogs (VDAs), and excessive PTH suppression. Increased patients' age, diabetes mellitus, and peritoneal dialysis as renal replacement therapy were found to be important contributors too. All possible factors leading to AD are listed in **Table 7**.

Iatrogenic factors
• Excessive vitamin D treatment
• Excessive calcium binders use
• Excessive PTH suppression
• High calcium concentration in dialysate fluids
• Peritoneal dialysis
• Aluminum treatment
Other factors
• Diabetes mellitus
• Age
• Hypogonadism
• Malnutrition
• Low thyroid hormone levels
• Altered growth factors and cytokines
• Vitamin D receptor polymorphisms

Table 7. Factors for adynamic bone disease in CKD.

Similarly to HTMBD, the symptoms in AD are nonspecific. In most of the cases the disease is asymptomatic, pain in the bones, fractures, and bone deformities are one of the most common

symptoms. In addition, signs of hypercalcemia, extraskeletal calcifications, and pruritus are also present. In cases of aluminum-associated OM, anemia and dementia can be detected [47].

Bone imaging detects fractures, looser zones, deformities, osteoporosis, and osteopenia. Laboratory findings are the key to the differential diagnosis between HTMBD and LTMBD. In LTMBD, lower PTH and bone-specific AP are present, as well as higher calcium and low phosphate levels. However, high PTH in biopsy-proven AD can be detected; therefore, PTH levels cannot be regarded as the best marker of differentiation between LTMBD and HTMBD [48]. Yet, PTH and PAP are significantly lower in LTMBD and a downward trend in these parameters indicates development of AD [45]. The clinical, laboratory, and radiologic findings in LTMBD are summarized in **Table 8**.

Clinical presentation of LTMBD
Bone fractures
Arthralgia
Bone pain
Vomiting, nausea, hypertension (hypercalcemia)
Calciphylaxis
Pruritus
Aluminum toxicity—anemia, dementia
Laboratory in LTMBD
Serum calcium—early stages N/↑; advanced stages - ↑↑
Serum phosphate—early stages N/↓; advanced - ↓/↑
PTH—early stages N/↓; advanced - ↓
BAP—early stages N/↓; advanced - ↓
Radiology in LTMBD
Fractures
Looser zones
Bone deformities
Osteopenia and osteoporosis

Abbreviations: PTH, parathyroid hormone; BAP, bone-specific alkaline phosphatase; N, normal; ↓, decreased; ↑, increased.

Table 8. Clinical presentation, laboratory, and radiologic findings in low turnover mineral bone disease (LTMBD).

3.2.4. Soft tissue and vascular calcifications

Soft tissue calcification is the third component of the diagnosis of CKD-related mineral bone disease and is more prevalent in CKD patients compared to the general population [49]. The most dangerous locations of extraskeletal calcification are the vasculature and the heart, increasing the risk for cardiovascular event. In renal disease, the pathogenesis of the deposits is not only passive deposition of calcium and phosphate, but also involves active cellular osteogenic transformation [50].

3.3. Pleiotropic effects in CKD patients

Poorer VD status is associated with a broad spectrum of nonskeletal clinical effects, probably due to the widely spread VDR and the presence of nonrenal 1-α hydroxylase. As already mentioned, VD is linked to renin-angiotensin aldosterone system suppression, renal protection, antiproteinuric effects, improved diabetes control, and reduced cancer risk. Pleiotropic effects were detected in CKD patients too—treatment with VD and vitamin D analogs in patients with renal disease led to reduced proteinuria; similar findings were reported in patients with diabetic nephropathy with a relatively low risk for hypercalcemia [51, 52]. However, the studies dealing with CKD patients are relatively few, compared to those reporting VD pleiotropy in the general population. Furthermore, no clear-cut data is present what VD treatment dose and target levels are needed to achieve the extraskeletal effects.

4. Vitamin D treatment in renal disease

The major directions in treating CKD-MBD are reducing phosphate levels, controlling PTH, and treatment of bone changes with bisphosphonates and other medications. Vitamin D preparations are used mainly in suppression of secondary hyperparathyroidism.

4.1. Vitamin D preparations

There are three types of vitamin D preparations used in CKD patients: native cholecalciferol/ergocalciferol, which is the form of vitamin D prior to hydroxylation in the liver and kidneys; calcitriol, which is the active form of vitamin D (dihydroxyvitamin D, 1,25VD) and vitamin D analogs. Vitamin D analogs are artificially synthesized molecules, aiming at reducing the side effects of calcitriol—hypercalcemia and hyperphosphatemia—while preserving its ability to suppress PTH. By changing the original structure of calcitriol modified affinity for VDR and vitamin D responding elements in the nucleus is created [53]. The most widely used analogs are doxercalciferol, paricalcitol, alfacalcidol, falecalcitriol, and 22-oxacalcitriol (maxacalcitol).

4.1.1. Cholecalciferol/ergocalciferol (nutritional vitamin D)

Cholecalciferol is the parent vitamin D, synthesized in the skin, known also as vitamin D3. Ergocalciferol is known as vitamin D2, and is detected in certain vegetable foods, whereas

vitamin D is found in fish oils and other foods of animal origin. Both vitamin D3 and vitamin D2 have equal biological activity.

Low 25VD levels are widely detected in CKD. In patients with CKD stages 3–5 not on dialysis supplementation with cholecalciferol/ergocalciferol is suggested as initial treatment of secondary hyperparathyroidism, as well as calcium supplementation and controlling phosphate levels [21]. Different dosing regimens have been suggested. In a study by Kooienga et al., 800 IU cholecalciferol with calcium supplementation was found effective in improving vitamin status and lowering PTH levels in elderly women with different GFR categories. However, it was impossible to differentiate the effect of vitamin D from that of calcium [54]. In another study, vitamin D2 supplementation according to the National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) protocol effectively suppressed PTH and improved 25VD level [55].

4.1.2. Calcitriol and vitamin D analogs (VDAs)

Treatment with calcitriol and VDAs is preserved for more advanced stages of secondary hyperparathyroidism, in cases with optimal 25VD level (above 75 nmol/l) with progressively rising or persistently high PTH and in patients on dialysis [21, 56]. The KDIGO group on CKD-MBD assessed the effect of the treatment on these four groups of indicators: patient-centered indicators—mortality, morbidity, and cardiovascular/cerebrovascular events; vascular calcifications; bone histology; and biochemical endpoints—PTH, calcium, phosphate, and BAP levels. In order to present the issue more clearly, we will present the data for predialysis patients and patients on dialysis.

4.1.2.1. Patients with CKD stages 3–5, not on dialysis

Patient-centered endpoints. There are several studies suffering from serious methodological limitations. Thus, no clear-cut can be made for this group of indicators.

Vascular calcifications. No study assessed the effect of cacitriol/VDA on vascular calcifications.

Bone morphology. Nordal and Dahl reported of improved histology in patients with osteitis fibrosa when treated with calcitriol. However, adynamic bone disease was not discussed in the paper, which is a major limitation of the study [57]. Hamdy et al. reported of improved findings in patients with osteitis fibrosa in cases treated with alfacalcidol versus placebo. In the treated group higher incidence of AD was detected [58].

Biochemical endpoints. Treatment with calcitriol, doxercalciferol, paricalcitol, and alfacalcidol effectively reduced PTH levels in renal patients [57–60] versus placebo. Similar findings were reported for BAP [54, 55]. Calcium significantly increased in the treated group with alfacalcidol and calcitriol, whereas paricalcitol and doxercalciferol therapy was associated with upward trend for calcium and calcium-phosphorus product. No difference between active and placebo arms was detected for hyperphosphatemia in doxercalciferol and paricalcitol trials [59, 60].

4.1.2.2. Patients on dialysis

In this patients group, the suggested target level of PTH is 2–9 times the upper normal limit for the assay [21]. The KDIGO group recommends that calcitriol or VDA treatment initiation and monitoring should be based on PTH, calcium, and phosphate level.

Patient-centered endpoints. Currently, no randomized controlled trials (RCT) have assessed the benefit from calcitriol/VDA treatment on mortality and other patient-centered indicators in dialysis patients. There are several observational trials with conflicting results. Treatment with calcitriol/VDA led to lower mortality compared to patients without treatment; use of paricalcitol and doxercalciferol was found superior to calcitriol in hemodialysis patients, with no difference detected between the two types of VDA [61]. Another study also reported superiority of paricalcitol over calcitriol [62]. However, these findings were not confirmed by the Dialysis Outcomes and Practice Patterns Study (DOPPS) analysis in 2009 [63]. Definitely, RCT are needed to evaluate the effect of calcitriol/VDA treatment on mortality.

Vascular calcification. Currently, there are not sufficient trials performed with endpoint soft tissue calcification; therefore, no recommendations have been formed [21].

Bone morphology. In two interventional studies, treatment with calcitriol versus placebo was assessed both in adults and children. Calcitriol significantly improved bone morphology in cases with osteitis fibrosa, but was associated with lower bone turnover and increased risk for AD [64, 65].

Biochemical endpoints. Treatment with VDA and calcitriol significantly reduced PTH and BAP in dialysis patients [64]. VDA were equivalent or superior to calcitriol in reducing PTH, with lower incidence of hypercalcemia and hyperphosphatemia [66]. Comparing the route of administration, the reports are conflicting. A meta-analysis reported of superiority of intravenous over oral vitamin D treatment [67]. Once the higher doses of intravenous vitamin D were removed, there were no differences in PTH suppression [68].

4.2. Monitoring vitamin D therapy

The major indicators for the effect of treatment are PTH and BAP, whereas calcium and phosphate are used mainly for assessing the risk for adverse events.

4.2.1. Patients with CKD stages 3–5, not on dialysis

In this group of patients, the target PTH value is not known. As already mentioned, in cases of elevated PTH, calcium, phosphate, and 25VD levels should be corrected first. If these measures fail VDA/calcitriol may be initiated. In these cases, calcium and phosphate levels follow-up is indicated. According to NKF-KDOQI guidelines, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter [56]. If trends for hypercalcemia and hyperphosphatemia occur dose of VDA/calcitriol should be adjusted or stopped.

4.2.2. Patients on dialysis

The target PTH values in dialysis patients range between 2 and 9 times the normal values [21]. In cases of rising or persistently high PTH, VDA/calcitriol treatment should be initiated. Treatment choice, however, should take calcium and phosphate level into consideration, as present hypercalcemia and hyperphosphatemia are contraindications for vitamin D sterol treatment. In cases where PTH level drops below the target value, or hypercalcemia/hyperphosphatemia develop, VDA/calcitriol treatment should be stopped or dose should be reduced. A possible frequency for testing calcium, phosphate, and PTH in these patients is suggested by NKF-KDOQI, serum levels of calcium and phosphorus are to be monitored at least every 2 weeks for 1 month and then monthly thereafter. Plasma PTH should be measured monthly for at least 3 months and then every 3 months once target levels of PTH are achieved [56].

4.2.3. Adverse effects from vitamin D treatment

The major problems in using vitamin D preparations (native vitamin D, calcitriol, VD analogs) are oversuppression of PTH, hypercalcemia, and hyperphosphatemia. These laboratory findings are the basis for increased AD in recent years. Therefore, regular control of PTH, serum calcium, and phosphorus levels is warranted as directed by the NKF-KDOQI guidelines. Other adverse possible events are associated with vitamin D toxicity (weakness, metallic taste, weight loss, muscle or bone pain, constipation, nausea, vomiting) and hypercalcemia (nausea, vomiting, loss of appetite, weight loss, constipation, increased thirst or urination, confusion). Other possible complications associated with VD analogs are chills and flu-like symptoms. However, these events are rare—none were detected in our everyday practice with native VD/calcitriol/VDAs.

4.3. Cost-effectiveness of VD treatment

Treatment with vitamin D analogs is an expensive issue, especially compared to the price of native vitamin D. Therefore, prior to VDAs and calcitriol, the first steps to be performed in the treatment of secondary hyperparathyroidism is correction of hyperphosphatemia (reduction of oral intake, calcium phosphate binders if applicable), hypocalcemia, and vitamin D insufficiency. If PTH is progressively rising, calcitriol/VDAs can be initiated [21].

5. Vitamin D metabolism after kidney transplantation

5.1. Impaired vitamin D metabolism after kidney transplantation: prevalence and pathophysiology

Suboptimal VD levels are commonly detected in kidney transplant recipients (KTRs), with prevalence of VD sufficiency below 20% [69]. Similar findings were detected in our institution in patients with duration of kidney transplantation (KTx) more than 6 months (n = 289), [70], **Figure 4**.

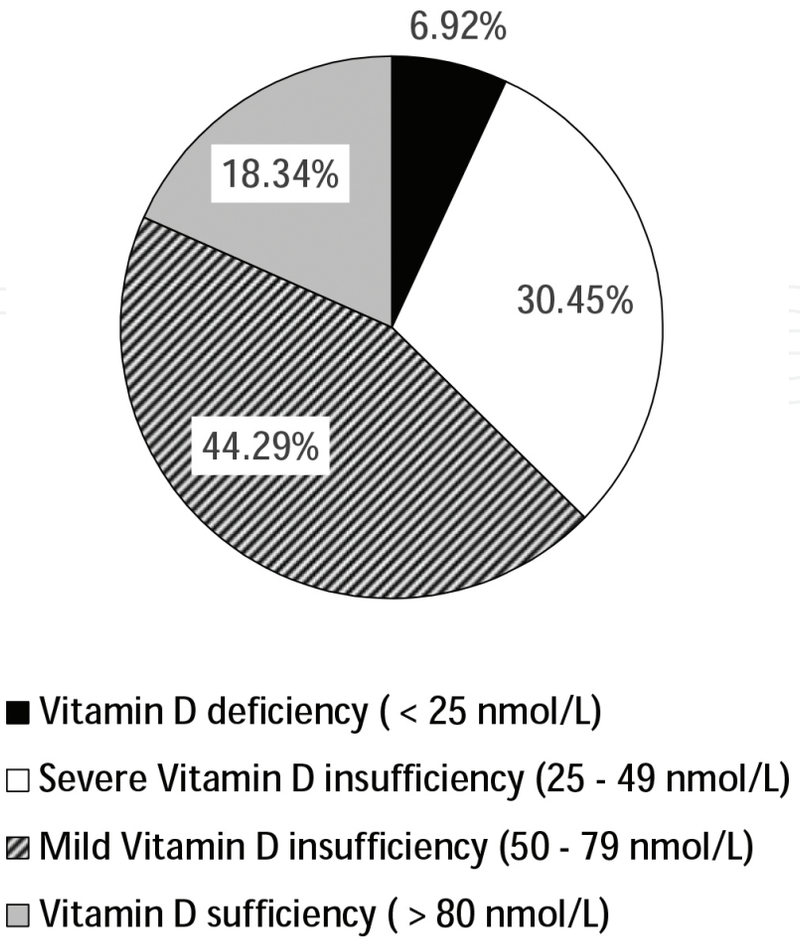

Figure 4. Prevalence of suboptimal 25-hydroxyvitamin D levels in Bulgarian kidney transplant recipients, *n* = 289. Filipov et al.

During winter-spring fall, during the annual nadir of 25VD, the share of VD sufficient KTRs follow-up in our center dropped to 2.59% [71].

The marked impairment of VD axis after KTx can be explained with transplantation-specific and CKD-related issues. The transplantation-related ones are sun exposure avoidance in order to minimize the risk for skin cancer, immunosuppressive treatment (steroids, calcineurin inhibitors), new onset diabetes after transplantation (NODAT), and higher incidence of obesity after KTx. The CKD-related causes for poor VD status were already outlined. The prevalence of CKD stage 3 and over in our department ranges between 49 and 58% over the last 4 years, which is in accordance with or even better than the results of other centers [72, 73]. **Table 9** summarizes the possible causes of VD insufficiency after KTx with the possible pathophysiological mechanisms involved.

5.2. Vitamin D after kidney transplantation: clinical implications

There are two basic aspects of vitamin D insufficiency after kidney transplantation—post-transplant mineral bone disease (PTx-MBD) and vitamin D pleiotropy.

Cause	Mechanism
Increased CKD prevalence	Reduced skin synthesis, reduced protein intake
Reduced sun exposure	Reduced skin synthesis
Use of sun-protecting cosmetics	Reduced skin synthesis
Proteinuria	Increased urine loss
NODAT	Decreased intestinal resorption
Higher prevalence of obesity	Reduced bioavailability
Steroids	Increased catabolism
Other immunosuppressive agents – CNI, MMF	Increased catabolism/suppressed liver synthesis

Abbreviations: CNI, calcineurin inhibitors; MMF, mycophenolate mofetil; NODAT, new onset diabetes after transplantation.

Table 9. Causes for vitamin D insufficiency after kidney transplantation.

5.2.1. Posttransplant mineral bone disease

After Ktx, PTx-MBD develops at the background of CKD-MBD, and consist of the same three components—biochemical abnormalities, bone pathology, and vascular/soft tissue calcifications. Poor vitamin D status is one of the factors for developing PTx-MBD, together with immunosuppressive therapy, persistent hyperparathyroidism, malnutrition, persistent CKD, hypogonadism, metastatic cancer disease, smoking, duration of dialysis and transplantation, cumulative steroid dose, diabetes, etc.

Biochemical abnormalities. Calcium levels tend to rise and phosphate usually decreases below normal values due to elevated PTH. These parameters should be monitored weekly during the first month posttransplant. PTH starts to decrease after successful KTx, but persistent hyperparathyroidism can be present in up to 43% after the first year [74]. Similar findings (33.69%) were detected in our center, coupled with persistent hypercalcemia or hypophosphatemia. Urine levels of phosphate and calcium were not evaluated routinely in our patients. Vitamin D levels normalize later—around 18 months after KTx [75]. After the early posttransplant period (up to 3 months after transplantation), regular follow-up of the parameters should be based on kidney function and the trends of the values. KDIGO suggested frequency of testing for KTRs similar to the one for pretransplant CKD patients (Table 4). In our center, during the first month calcium and phosphate are monitored once weekly, with gradually decreasing the frequency until the suggested values are reached; 25-hydroxyvitamin D levels are monitored at least twice annually, taking into consideration its seasonal variations.

Bone. Rapid reduction in bone density is widely reported, with faster bone loss during the first months after successful KTx, though reduced bone density loss was reported years after the operation [76]. The factors contributing to posttransplant bone disease were already listed.

A major complication is increased fracture risk, associated with increased morbidity and mortality.

Vascular calcification. Assessing the development of soft tissue calcification is difficult due to the high prevalence of vascular calcification in advanced CKD. Only one study demonstrated possible slowing of calcification process after KTx [77]. Therefore, currently there is paucity in scientific data for this problem.

5.2.2. Vitamin D pleiotropy after kidney transplantation

With the advance of transplantology, short-term kidney survival has improved significantly over the last decades. However, long-term graft survival still remains a problem, hardly exceeding 70–80% survival at the 10th year after the operation. The major reasons for late graft loss are death of the patient due to cardiovascular disease (CVD), malignancy, and infection; also, calcineurin toxicity and chronic rejection are also other significant causes. The already mentioned pleiotropic effects of VD were described mostly in the general population or CKD patients. It can be expected that these properties can improve patient- and graft-targeted outcomes.

5.2.2.1. Vitamin D and diabetes mellitus after kidney transplantation (KTx)

New onset diabetes after transplantation (NODAT) is associated with higher morbidity and mortality after transplantation, and is linked to the use of steroids and calcineurin inhibitors after the operation. Many experimental and animal studies indicate that better vitamin D status is associated to improved insulin secretion and insulin resistance. Several human studies report of inverse correlation between 25VD level and diabetes prevalence [78, 79]. The data after solid organ transplantation are scarce. Our findings do not show any link between 25VD level and glycemic control [80], thus not supporting any association between VD status and glycemia after KT. No interventional studies assessed the effect of VD supplementation or use of calcitriol/VD analogs in solid organ transplantation patients on diabetes prevalence after the procedure [81].

5.2.2.2. Vitamin D and cardiovascular risk after KTx

The risk for cardiovascular disease (CVD) is increased after transplantation compared to the general population [82]. Low vitamin D levels were associated with arteriosclerosis and endothelial dysfunction in end-stage renal patients [83]. Other studies also reported of increased CVD incidence in poor VD status. A possible explanation may be that VD-receptor activation in the cardiomyocytes suppresses their proliferation. However, the studies after solid organ transplantation are lacking. Furthermore, higher doses of vitamin D may be associated with increased risk for vascular calcifications [84].

5.2.2.3. Vitamin D and malignancy after KTx

Malignancy is one of the major contributors to patient and graft loss after transplantation, especially in the long run. Several studies reported lower prevalence of different types of

neoplasia in subjects with better VD status [85, 86]. The findings were detected in renal transplant patients [87], though the results should be confirmed by prospective studies, as some reports indicate that high 25VD may increase the risk for prostate neoplasia [88].

5.2.2.4. Vitamin D and infection after KTx

Infections play a key role for mortality and morbidity after transplantation. Experimental studies have shown that macrophages express VD receptor and its activation leads to increased antimicrobial activity of the macrophages [89]. Human studies also report of beneficial effect of better VD status on infection prevalence. However, only one trial has demonstrated inverse correlation between 25VD and infection rate in lung transplant patients [90]. Vitamin D had no influence on urinary tract infection rate in Bulgarian KTRs followed-up in our center [91]. Therefore, further studies are needed to evaluate the association between VD and infection after transplantation.

5.2.2.5. Vitamin D and rejection after KTx

Rejection episodes are still a matter of concern and linked to reduced graft survival. On the other hand, long-term immunosuppression contributes to serious adverse events. Higher 25VD was related to lower rejection incidence in KTRs [92]. Experimental reports indicate that calcitriol suppresses T-cell activity and proliferation, as well as B-lymphocyte proliferation, IgG secretion, and major histocompatibility complex class II expression [93–95]. In two small prospective studies, calcitriol treatment was found to have significant immunomodulatory effect [96, 97]. However, the trials in transplant patients are small and single centered, and further research is needed.

5.2.2.6. Vitamin D and renoprotection after KTx

The effect of VD on renal protection has been described earlier in this chapter together with the possible mechanisms and experimental data supporting them. In the setting of renal transplantation, low VD was associated with higher proteinuria [98]. In addition, calcitriol therapy was found beneficial for renal graft function [99]. However, in a small prospective study by Courbebaisse et al. biopsy findings were compared between cholecalciferol-treated KTRs and KTRs without supplementation. The findings did not demonstrate significant difference in terms of interstitial fibrosis and tubular atrophy [100]. Due to the small number of trials and their small size conclusions cannot be drawn.

5.2.2.7. Vitamin D and mortality after KTx

Better VD status was associated with lower mortality in the general population and CKD patients, including patients on hemodialysis [98–100]. However, there are no data in terms of mortality in patients after renal transplantation.

In summary, the data for VD pleiotropy after renal transplantation are relatively scarce, originate from single-center studies, and usually with small number of patients. Therefore, further studies including prospective interventional ones are needed.

5.3. Vitamin D treatment after KTx

The influence of vitamin D treatment after KTx was mainly assessed for its effect on biochemical abnormalities in calcium phosphorus metabolism. The data about the effect on fracture risk, bone density, and pleiotropy are still insufficient. Guidelines are available only for the first posttransplant year. The data for the treatment after the first year are insufficient [21].

5.3.1. Native vitamin D (cholecalciferol/ergocalciferol)

Cholecalciferol supplementation effectively suppressed PTH in renal transplant patients [101]. A meta-analysis performed by KDIGO showed improved bone density in patients with cholecalciferol-/ercalciferol-treated KTRs versus KTRs without VD supplementation [21]. The suggested cholecalciferol dose corresponds with the recommended dose for the general population [21]. As no data are present for patient-targeted endpoints such as fracture risk, no guidelines are available for this issue. Similarly, no specific recommendations can be given for VD pleiotropy. However, there are two large randomized trials assessing cholecalciferol supplementation in KTRs and its effect on renal graft function, NODAT incidence, infection risk, cancer prevalence, and mortality after KTx [82].

5.3.2. Calcitriol/vitamin D analogs

Treatment with calcitriol/VDAs in renal transplant patients with CKD stages 3T–5T is based on the same principles as in patients with CKD stages 3-5 (GFR below 60 ml/min). The reason for accepting the same approach is the paucity of RCTs in KTRs treated with calcitriol/VDAs [21]. However, certain considerations should be taken into account. The most important one is the high prevalence of persistent hyperparathyroidism and hypercalcemia after KTx. If the PTH levels do not resolve parathyroidectomy should be considered in these cases. As already mentioned, further research is needed in terms of pleiotropic effects of calcitriol/VDA treatment in KTRs.

5.3.3. Treatment monitoring in transplant recipients

Similarly to pretransplant CKD stages, monitoring calcium, phosphate, PTH, bone AP, and 25-hydroxyvitamin D depends on the renal function, the trend in biochemical abnormalities, and the intervention performed. Still, certain frequencies are suggested (**Table 4**) after the first 3 months posttransplant.

6. Conclusion

Vitamin D metabolism is significantly impaired at different levels in the early stages of renal disease. The influence of the abnormalities spans beyond calcium-phosphorus metabolism, having impact on mortality, cardiovascular morbidity, cancer risk, renal protection, etc. Thus, VD metabolites have pivotal role in controlling a great number of intracellular pathways that are impaired in renal disease contributing to poorer patient outcomes.

However, there are still problems to be clarified: the dose of vitamin D supplementation, target levels of 25-hydroxyvitamin D and PTH in predialysis patients, possible biochemical abnormalities due to treatment (hypercalcemia, hyperphosphatemia), and vitamin D pleiotropy in CKD patients prior and after kidney transplantation. The great number of unsettled problems in this sphere and its great potential for improving patient outcomes guarantee that vitamin D will be a "hot topic" in the world of renal disease over the next years.

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