



Ukrainian Journal of Nephrology and Dialysis

Scientific and Practical, Medical Journal

Founder:

- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: <https://ukrjnd.com.ua>

Research article

Selinay Demirel, Murat Gürbüz

doi: 10.31450/ukrjnd.1(81).2024.09

The role of native vitamin D treatment in the clinical assessment of osteoporosis in patients with chronic kidney disease

Department of Nutrition and Dietetics, Trakya University, Edirne, Turkey

Citation:

Demirel S, Gürbüz M. The role of native vitamin D treatment in the clinical assessment of osteoporosis in patients with chronic kidney disease. Ukr J Nephrol Dial. 2024;1(81):71-85. doi: 10.31450/ukrjnd.1(81).2024.09.

Article history:

Received November 18, 2023

Received in revised form
December 01, 2023

Accepted December 02, 2023

Abstract. *The prevalence of vitamin D deficiency is high in patients with chronic kidney disease (CKD). Vitamin D deficiency is associated with various bone disorders such as osteoporosis by affecting bone mineralization. Current international guidelines recommend vitamin D supplementation in CKD as well as in the general population. However, the effect of various forms of vitamin D on bone health in CKD remains unclear. Few randomized controlled studies have evaluated the effects of vitamin D supplementation on bone mineral density and bone turnover markers; however, the findings of these studies are heterogeneous. This review aimed to present comprehensive and current findings on the effects of native vitamin D supplementation on bone biomarkers and bone mineral density in CKD. We inferred that native vitamin D treatment could improve some bone biomarkers, particularly in predialysis CKD patients with severe vitamin D deficiency. Our findings also draw attention to the fact that vitamin D is an important factor in treatment. However, it is essential to design better-quality and comprehensive controlled studies to obtain clear findings.*

Keywords: osteoporosis, vitamin D, Calcitriol, renal osteodystrophy, calcidiol.

Conflict of interest. The authors declare no conflict of interest.

© S. Demirel, M. Gürbüz, 2024.

Correspondence should be addressed to Murat Gürbüz: muratgurbuz@trakya.edu.tr



© Демірель С., Гюрбюз М., 2024

УДК: 616.61-036.12: 616.71-007.234]-085

Селінай Демірель, Мурат Гюрбюз

Роль лікування вітаміном D у клінічній оцінці остеопорозу у хворих на хронічну хворобу нирок

Кафедра харчування та дієтології Тракійського університету, Едірне, Туреччина

Резюме. *Поширеність дефіциту вітаміну D є надзвичайно високою серед пацієнтів з хронічною хворобою нирок (ХХН). Дефіцит вітаміну D асоційований з мінерально-кістковими розладами, в тому числі й остеопорозом. Сучасні міжнародні настанови рекомендують додатковий прийом вітаміну D хворим на ХХН та серед населення в цілому. Проте вплив різних форм вітаміну D на здоров'я кісток у пацієнтів з ХХН залишається неясним. Кілька рандомізованих контрольованих досліджень оцінювали вплив прийому вітаміну D на мінеральну щільність кісткової тканини та маркери обміну кісткової тканини; однак результати цих досліджень неоднорідні. Цей огляд мав на меті представити всеосяжні та сучасні результати щодо впливу нативних добавок вітаміну D на кісткові біомаркери та мінеральну щільність кісткової тканини у хворих на ХХН. Ми прийшли до висновку, що лікування вітаміном D може покращити деякі біомаркери кісток, особливо у пацієнтів з ХХН на переддіалізній стадії, із серйозним дефіцитом вітаміну D. Наші висновки також привертають увагу до важливості застосування вітаміну D у лікуванні хворих на ХХН. Однак для отримання чітких висновків важливо розробити якісні та комплексні контрольовані дослідження.*

Ключові слова: *остеопороз, вітамін D, кальцитріол, ниркова остеодистрофія, кальцидіол.*

Introduction. Chronic kidney disease (CKD) is a progressive disease in which kidney function is irreversibly impaired because of certain changes in kidney function or structure [1]. According to the Kidney Disease Improving Global Outcomes (KDIGO) reports, CKD affects 10–15% of the total population worldwide [2]. In Turkey, the prevalence of CKD is 15.7%, according to the reports of the Chronic Renal Disease in Turkey (CREDIT) study [3]. However, it is known that the actual prevalence is difficult to estimate due to low awareness levels and limited access to laboratory services. Hypertension, diabetes mellitus (DM), obesity, and primary kidney diseases are serious health problems that can cause significant complications such as CKD. It has been reported that cardiovascular disease (CVD) is primarily responsible for mortality and morbidity, and the risk of comorbidity and cardiovascular mortality is lower in women [4]. There is an inverse relationship between glomerular filtration rate (GFR) and CVD risk, regardless of sex, age, or other risk factors [5]. CKD significantly increases global health care costs. In high-income countries, more than 3% of the annual health-care budget is spent solely on the treatment of end-stage renal disease (ESRD) [6]. In Turkey, it is estimated that this rate corresponds to approximately 5% of the total health budget [7].

In the initial stages of CKD, systemic mineral metabolism and bone tissue composition begin to change

with decreased kidney function. As kidney dysfunction progressively increases, deteriorating mineral metabolism causes bone disorders, defined as renal osteodystrophy [8]. Renal osteodystrophy is expressed as a component of the syndrome called Chronic Kidney Disease-Mineral and Bone Disorders (CKD-MBD), which causes bone fractures, vascular calcification and mortality. However, moderate and advanced CKD patients are usually elderly individuals and may also experience age-related or post-menopausal osteoporosis alongside declining kidney function [9]. Osteoporosis is a progressive bone disease that results in increased bone fragility due to low bone mineral density (BMD) and deterioration of the microarchitecture of bone tissue [8]. It is known that the factors such as age, gender, glucocorticoid use, malnutrition, physical inactivity and vitamin D deficiency contribute to the occurrence of osteoporosis in CKD patients [8, 10]. Osteoporosis often coexists with CKD, and the global prevalence of both is increasing day by day. Osteoporotic fractures, which cause increased disability and reduced survival, cost 5.8 million disability-adjusted life years (DALYs) annually worldwide [9].

Sustaining calcium and phosphorus metabolism is possible by maintaining vitamin D homeostasis in the body. The level of circular vitamin D is maintained by the production of active vitamin D (calcitriol) in the kidney. In this context, a better understanding of the relationship between renal damage and impaired vitamin D homeostasis may offer important clinical advantages [11, 12]. It is known that vitamin D has an important role in the maintenance of mineral balance and bone tissue health, as well as in the prevention of health problems, such as cardiovascular damage, renal damage, hyperparathyroidism, and immune dysfunction [11, 13, 14]. Vitamin D is defined as a steroid

Murat Gürbüz

muratgurbuz@trakya.edu.tr

hormone that is exogenously supplied with animal- or plant-based foods or nutritional supplements and synthesized endogenously from subcutaneous cholesterol [15]. Studies have shown that the prevalence of vitamin D deficiency is high in patients with CKD and that this deficiency increases disease progression [16, 17]. This vicious cycle leads to osteoporosis and/or bone fractures due to the increasing severity of CKD. It is well known that the prevalence of fractures is higher in patients with CKD compared with the general population [18]. At this point, there is some evidence that BMD and bone formation markers may be improved by native vitamin D treatment [19, 20]. However, there are no clear findings on the role of native vitamin D in the prevention and/or treatment of osteoporosis in patients with CKD. This review aimed to comprehensively investigate the effect of native vitamin D treatment on bone mineral density and biochemical parameters used in the clinical assessment of osteoporosis in patients with CKD.

Overview of vitamin D metabolism. Vitamin D is a nomenclature expressing the group of fat-soluble steroidal compounds that regulate the absorption and metabolic effects of calcium and phosphate [12]. In nature, vitamin D exists in two different forms as vitamin D3 (cholecalciferol) in animal tissues and vitamin D2 (ergocalciferol) in plant tissues. Despite dietary sources such as animal- and plant-based foods, the main source of vitamin D in the body is subcutaneous 7-dehydrocholesterol. As a classical metabolic pathway, vitamin D3 is converted from 7-dehydrocholesterol to previta-

min D3, followed by vitamin D3 by thermal isomerization under the effect of ultraviolet B (UVB) rays in the epidermis [21]. Vitamin D3, which is supplied by diet or synthesized in the skin by UVB rays, is transported to the liver by binding to vitamin D-binding protein (VDBP) in the bloodstream. In the liver, it is converted to 25-hydroxy vitamin D [25(OH)D], also known as calcidiol, by 25-hydroxylase (CYP2R1) and sterol 27-hydroxylase (CYP27A1), which is then converted to 1,25-dihydroxy vitamin D [1,25(OH)2D], also known as calcitriol, in the proximal tubule of the kidney by 1- α -hydroxylase (CYP27B1) [21]. Calcitriol is the most active form of vitamin D and is transported to the target organs via VDBP after synthesis [12]. Calcitriol exerts its effects on target cells through the vitamin D receptor (VDR), which is found in almost all cells in the human body and can activate approximately 3% of the human genome. The calcitriol/VDR complex formed by the binding of calcitriol to VDR in the cytoplasm enters the nucleus and binds to the retinoid X receptor (RXR). This complex interacts with vitamin D response elements to up-regulate or down-regulate the transcription of target genes [22].

The main endocrine function of calcitriol is to help maintain regular calcium homeostasis by increasing intestinal calcium absorption, stimulating calcium resorption from the bones, and increasing calcium reabsorption in the distal tubule of the kidney [21]. Calcitriol synthesis occurs under tight control of the kidneys (Fig. 1) [23].

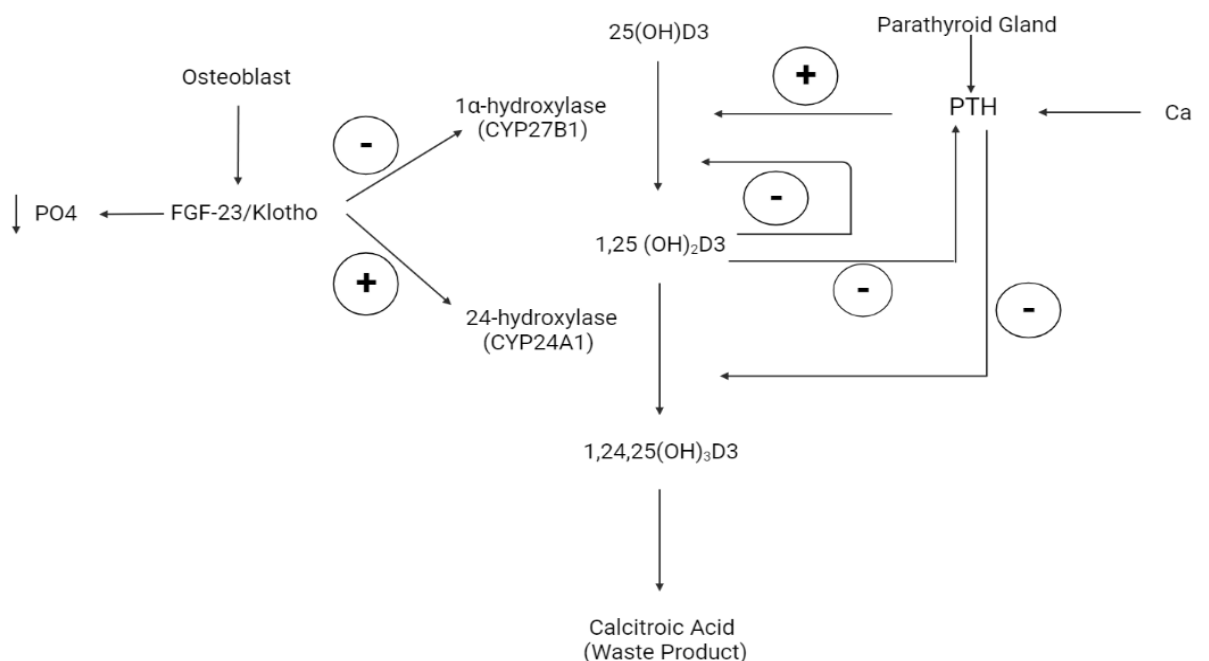


Fig. 1. Illustration of vitamin D synthesis in the kidney: Native vitamin D is converted to 25(OH)D by hepatic 25- α -hydroxylase. Renal (mostly) and extrarenal 1- α -hydroxylase converts 25(OH)D to the active form, 1,25(OH)2D. While PTH increases vitamin D activation by up-regulating 1- α -hydroxylase in proximal tubular cells, FGF23 inhibits vitamin D activation by down-regulating 1- α -hydroxylase and up-regulating 24- α -hydroxylase. FGF-23: Fibroblast growth factor-23; PTH: Parathyroid hormone; Ca: Calcium; PO4: Phosphate.

In hypocalcemia, parathyroid hormone (PTH) secretion is stimulated by calcium-sensitive receptors (CaSR) in the parathyroid gland; thus, calcitriol production increases with PTH-mediated CYP27B1 stimulation. Calcitriol sensitizes the parathyroid gland to calcium inhibition by increasing serum calcium levels, thereby inhibiting PTH secretion. Calcitriol can also suppress its own production by inhibition of CYP27B1 and stimulate its own degradation through induction of 24-hydroxylase (CYP24A1) in the kidneys [23]. Further, it is known that the expression of fibroblast growth factor-23 (FGF-23) secreted mainly by osteoblasts and osteocytes can be stimulated by calcitriol. In addition, increased serum calcium levels can increase FGF-23 synthesis independent of serum vitamin D and PTH levels [24]. FGF-23 not only stimulates renal phosphate excretion, but also suppresses calcitriol synthesis through CYP27B1 inhibition and accelerates calcitriol degradation through CYP24A1 induction [23, 25].

Although it has many different metabolic roles, such as glucose homeostasis, cardiovascular health, immunomodulation and anti-proliferation, vitamin D exerts its main effect in bone tissue together with the actors such as PTH and FGF-23 [12, 26]. It has long been known that vitamin D has direct and indirect effects on bone formation through modulation of calcium and phosphate metabolism. Many studies have reported that vitamin D increases bone mineralization and is an important stimulator of bone remodeling [27, 28]. During the remodeling process, vitamin D not only regulates serum calcium and phosphate levels, but also stimulates the maturation and proliferation of VDR-expressing osteoblasts and osteoclasts [29]. Atkins et al. (2007) demonstrated that calcitriol up-regulates the bone formation marker genes such as osteocalcin, nuclear factor kappa- β ligand (RANKL), and osteopontin in human osteoblasts [30]. The effects of calcitriol on the regulation of calcium/phosphate metabolism and bone remodeling are summarized in Fig. 2 [31].

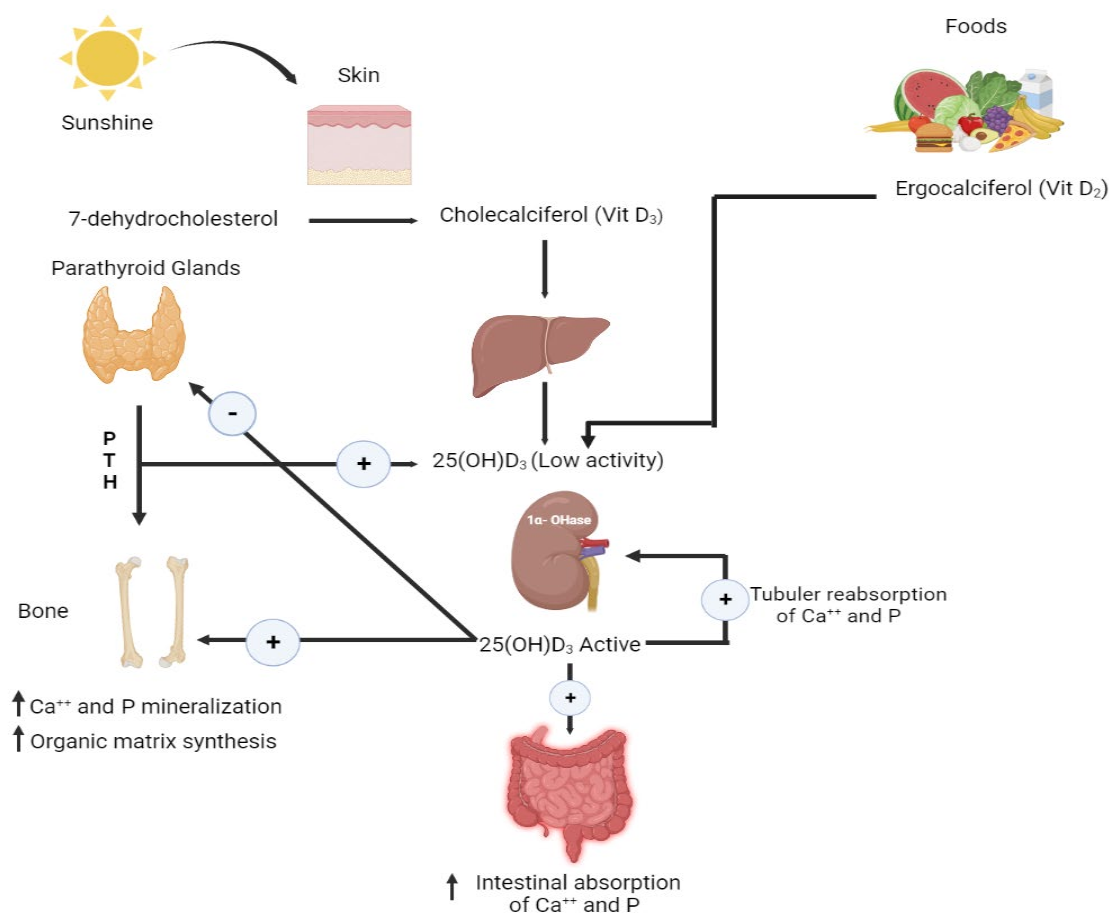


Fig. 2. Schematic summary of vitamin D metabolism and its mechanism of action: Vitamin D is derived from both ergocalciferol and cholecalciferol. Ergocalciferol derives from UV irradiation of ergosterol, the sterol in mushrooms, while cholecalciferol derives from UVB irradiation of 7-dehydrocholesterol in the skin. Calcitriol, the active form synthesized in the kidney, suppresses parathyroid hormone secretion, stimulates renal reabsorption and intestinal absorption of calcium and phosphorus. It also promotes bone remodeling by increasing circulating calcium and phosphate levels, and stimulating mineralization and organic matrix synthesis by maturation and proliferation of VDR-expressing osteoblasts and osteoclasts. Ca: Calcium; P: Phosphorus; PTH: Parathyroid hormone.

Vitamin D metabolism in CKD. CKD is one of the main causes of vitamin D deficiency, which is an important public health problem. CKD is an irreversible progressive loss of kidney function that persists for at least three months and eventually leads to ESRD.

Decreased kidney function can be determined by the estimated glomerular filtration rate (eGFR; 120 to 0 mL/min/1.73 m²) or the corresponding CKD stage (G1 to G5) [32]. GFR stages representing kidney function are shown in Table 1 [10].

Table 1

Glomerular Filtration Rate-based Disease Stages in CKD

CKD Stages	GFR mL/min/1.73m ²
G1	≥90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29
G5	<15
G5D	Dialysis

Abbreviations: GFR: Glomerular filtration rate; CKD: Chronic kidney disease

Literature findings have reported that decreased GFR level is associated with vitamin D deficiency [11, 16]. As seen in Figure 2, the conversion of calcidiol to calcitriol occurs in the kidney proximal tubule [31]. Therefore, it is well known that renal dysfunction alters vitamin D metabolism in CKD patients. Vitamin D deficiency is mainly due to decreased renal filtration of calcidiol, suppression of calcitriol synthesis by FGF-23 and uremic factors, and high urinary excretion of calcidiol in patients with CKD [32].

The FGF-23 level, which starts to increase in the early stages, is primarily responsible for the vitamin D deficiency in CKD. Hyperphosphatemia resulting from renal dysfunction stimulates FGF-23 expression in osteocytes and osteoblasts, and increased FGF-23 levels decrease renal phosphate reabsorption through NaPi-IIa inhibition and calcitriol synthesis through renal CYP27B1 inhibition [33]. Additionally, acidosis and hyperuricemia may also cause decreased calcitriol synthesis in patients with CKD [34, 35]. Vitamin D deficiency causes hypocalcemia, owing to its active role in the intestinal absorption and renal reabsorption of calcium. Hypocalcemia may cause secondary hyperparathyroidism (SHPT) in patients with CKD by triggering PTH secretion in the parathyroid gland [32]. Furthermore, it has been suggested that factors that decrease calcidiol bioavailability, such as decreased exposure to sunlight, insufficient dietary vitamin D intake, decreased glomerular filtration of calcidiol, and increased urinary excretion of calcidiol due to decreased megalin expression, may also cause vitamin D deficiency in patients with CKD [33].

Serum calcidiol level is considered to be the best indicator for the assessment of vitamin D status [33, 36]. Many authors believe that the lower limit of adequate calcidiol levels should be 30 ng/mL [33, 37]. According to the Korea National Health and Nutrition Examina-

tion Survey (KNHANES) reports, serum calcidiol levels decrease when GFR is below 60 ml/min/1.73 m². [38]. The literature shows that severe deficiencies begin to occur in patients with stage 3 CKD, and the deficiency becomes more severe in advanced stages [16, 39]. In hemodialysis patients, this deficiency reaches up to 80% [40]. Aging, corticosteroid use, and obesity have also been suggested to affect the vitamin D status in patients with CKD [9, 33, 37]. Although there is no international consensus regarding the optimal dose, most observational and randomized controlled studies have shown that nutritional vitamin D supplementation promotes bone health [19, 41]. However, the significant effect of vitamin D supplementation on bone health in all patients with CKD has not yet been determined. The Current KDIGO CKD-MBD Guidelines do not recommend routine vitamin D treatment for predialysis patients with stage 3a-5 CKD [42].

Bone metabolism and bone disorders in patients with CKD. In early-stage CKD, decreased expression of the co-receptor klotho causes increased serum FGF-23 levels and increased FGF-23 stimulates urinary phosphate excretion and decreases calcitriol synthesis through proximal tubular CYP27B1 inhibition [23]. Furthermore, increased levels of sclerostin and dickkopf-1 due to CKD progression reduce bone formation by inhibiting LRP5/6-mediated Wnt signaling and stimulating RANKL-mediated osteoclastogenesis [43]. Moreover, uremic toxins, such as indoxyl sulfate, which accumulate in tissues owing to increased levels of circular urea, can reduce PTH receptor expression in osteoblasts [44]. It is well known that the trend of increasing serum phosphate levels from the early stages in patients with CKD plays a central role in the occurrence of SHPT [32, 33]. These known factors reduce bone strength by causing abnormal bone remodeling and osteoporosis in patients with CKD [43, 44].

CKD is often associated with mineral and bone disorders, osteoporosis, and low trauma fractures [8, 18]. As renal function declines, CKD-MBD, which is an important complication, may occur in patients with CKD. This syndrome is defined as a systemic disorder of mineral and bone metabolism characterized by one or more anomalies such as impaired calcium, phosphorus, vitamin D and PTH metabolism; changes in bone mineralization, bone turnover, bone volume and bone strength; and soft tissue calcification [43]. It is well known that CKD-MBD significantly increases the risk of bone fractures, cardiovascular events, and mortality [9]. Renal osteodystrophy, which is characterized by detectable changes in bone morphology on biopsy, is expressed as a bone tissue-related subcomponent of CKD-MBD syndrome [9, 45]. Compared with the general population, patients with CKD are more likely to have bone fractures due to renal osteodystrophy. A prospective cohort study of stage 3-5 CKD patients has found a moderate association between CKD and high fracture risk, regardless of BMD, age, or race [46].

The etiology of the increased fracture risk in the CKD population is multifactorial. Many of the risk factors identified in the general population, such as early menopause, low BMD, family history of osteoporosis, low body mass index (BMI), and inflammatory diseases, increase the risk of fracture in patients with CKD [44, 47]. However, there is no clear distinction between fractures caused by severe osteoporosis or renal osteodystrophy. Therefore, the basic approach in fracture management is to reduce CKD-induced mineral and bone disorders and to treat osteoporosis [47]. KDIGO recommends the use of bone quality parameters such as turnover, mineralization, and volume determined by biopsy when evaluating bone pathology. Apart from bone biopsy, biomarkers such as bone specific alkaline phosphatase (BSAP) and intact PTH (iPTH) levels can also contribute to the assessment of bone turnover [43, 48]. In addition to quality parameters that directly assess fracture risk, noninvasive methods, such as BMD measurement, have also been defined. Many studies have reported that low BMD can predict fracture risk in the CKD population [49, 50]. However, routine BMD measurements are not recommended for predicting bone fractures in CKD patients [42].

The relationship between CKD and osteoporosis.

It has been reported that age-related or postmenopausal osteoporosis is mostly detected in patients with CKD [9]. The fact that the risk of osteoporosis is more than doubled in individuals aged 80 years and older compared to patients aged 70-79 reveals the importance of age in osteoporosis [51]. It is also known that decreased kidney function can cause abnormal bone remodeling and osteoporosis [44, 45]. The NHANES-III study results showed that the risk of osteoporosis was two times higher in CKD patients with a GFR less than 60 mL/min [52]. However, osteoporosis can also coexist with renal osteodystrophy or CKD-MBD, making the diagnosis of osteoporosis difficult [53]. The NHANES-III findings re-

ported that more than 60% of women with osteoporosis had stage 3 CKD, and 23% had stage 4 CKD [51].

Literature findings have suggested that there was a positive correlation between GFR and BMD in patients with CKD [54, 55]. BMD is often measured with Dual Energy X-ray Absorptiometry (DXA), despite some limitations such as only areal density assessment, and the results are expressed as T-scores. The World Health Organization (WHO) defines osteoporosis as a T-score ≤ -2.5 [9, 12]. While the WHO-recommended BMD criteria can be used for osteoporosis in patients with stage 1-3 CKD, these BMD criteria cannot be used unless other renal bone diseases are excluded owing to abnormal bone turnover in patients with stage 4-5 CKD [53]. It is known that all forms of severe renal bone disease are characterized by low BMD and high fracture risk from low trauma. Bone biopsy is considered the gold standard for elucidating histomorphometric abnormalities in patients with stage 3-5 CKD [48]. However, it is not widely used because it is time consuming, expensive, and not useful in predicting bone fractures. All forms of renal bone disease have been noted to have a component of osteoporosis, which includes microarchitectural deterioration according to the National Institutes of Health definition of osteoporosis [53]. Therefore, most studies have demonstrated an association between CKD and osteoporosis through BMD measurements and bone turnover biomarkers.

It has been reported that there is a significant relationship between the severity of CKD and the increasing severity of osteoporosis [56]. Observational studies have shown a high prevalence of osteoporosis, especially in ESRD patients receiving dialysis treatment [57, 58]. However, this prevalence is not significantly different between hemodialysis and peritoneal dialysis treatment [59, 60]. Most authors have associated low bone mass with old age, increased PTH levels, low BMI, high serum ALP levels, and low serum albumin levels in ESRD patients, regardless of the type of dialysis treatment [58, 60]. Additionally, Lv et al. (2023) associated an increased prevalence of osteoporosis in ESRD patients who were candidates for kidney transplantation with increased dialysis time [61]. The number of studies on the prevalence of osteoporosis in patients with CKD receiving peritoneal dialysis is negligible. It is of great importance to better understand the relationship between CKD and osteoporosis in further studies to determine treatment and reduce the burden of mortality/morbidity.

Dietary sources of vitamin D. The main source of vitamin D is cutaneous synthesis and its dietary sources are scarce. Dietary vitamin D has two different forms: ergocalciferol (vitamin D₂), found in mushrooms, and cholecalciferol (vitamin D₃), found in animal-based foods [62]. Dietary sources of vitamin D₃ include fish liver oil, oily fish (herring, tuna, and sardines) and egg yolk. Dietary sources of vitamin D₂ include mushrooms, vegetables, and foods fortified with vitamin D [63-65]. Dietary sources of vitamin D are as seen in Table 2 [65, 66].

Table 2

The amount of dietary vitamin D per 100 grams of food

Food Source	Vitamin D Content
Cod Liver Oil	10.000IU D3
Fresh Wild Salmon	600 – 1000IU D3
Canned Salmon	300 – 600 IU D3
Fresh Farm Salmon	100 – 250 IU D3
Canned Sardines	300 IU D3
Canned Mackerel	250 IU D3
Canned Tuna	230 IU D3
Fresh Shiitake Mushrooms	600 – 1000 IU D2
Sun Dried Mushrooms	1600 IU D2
Egg yolk	628 UI D3
Beef Kidney	45 IU D3
Beef Muscle	49 IU D3

The main source of vitamin D in Western countries is oily fish. Some countries have several policies to fortify foods, such as milk and dairy products, margarine, breakfast cereals, and fruit juices with vitamin D. Mushrooms that are dried in the sun and exposed to UV rays are also considered a primary dietary source of vitamin D, especially for vegans and vegetarians [62].

Inadequate sun exposure and dietary intake of vitamin D cause vitamin D deficiency. The definition of vitamin D deficiency varies according to various national and international organizations; however, general literature findings define a serum calcidiol level of <20-30 ng/mL as a vitamin D deficiency [33, 64]. An adequate intake (AI) for vitamin D is recommended as 15 ug/day for adults, children aged 1–17 years, and pregnant and lactating women by European Food Safety Authority (EFSA) [67].

The activity of native vitamin D supplementation on bone health in patients with CKD. All guidelines aimed at optimizing bone health recommend ensuring an adequate vitamin D status. Vitamin D supplementation has been reported to significantly reduce the risk of bone fractures in a population not screened for renal function, especially in elderly individuals with vi-

itamin D deficiency [68]. Vitamin D supplementation is considered essential for maintaining drug efficacy in osteoporotic patients using anti-resorptive drugs [69]. Although CKD is often associated with mineral and bone disorders, osteoporosis, and low-trauma fractures, randomized controlled trials on the role of vitamin D treatment in reducing fracture risk in patients with CKD are limited. Although serum calcidiol levels begin to decrease significantly from the onset of stage 3 CKD in patients, few studies on the effect of vitamin D treatment on bone health have presented heterogeneous findings. This review evaluated 13 different randomized controlled trials using cholecalciferol (eight studies), ergocalciferol (four studies), and extended release (ER) calcifediol (one study). The doses of vitamin D used were 1.200-8.000 IU per day, 6.000-50.000 IU per week, and 9000-50.000 IU per month, respectively. Only two studies used 300.000 IU of vitamin D once at the start of the study and then at week 8. Study duration was in the range of 5-52 weeks. The current study findings regarding the activity of vitamin D treatment in predialysis CKD patients and CKD patients receiving dialysis treatment are summarized in Tables 3 and 4, respectively.

Table 3

Vitamin D treatment and several biochemical markers for the clinical assessment of osteoporosis in predialysis CKD patients

Supplement Type	Dose	CKD Stage	Participants and Study Duration	Vitamin D Level	Results	Reference
Oral Cholecalciferol	300.000IU Once both at baseline and at 8 weeks	3 and 4	18-70 years old, non-diabetic subjects (n=120) 16 weeks	<20 ng/ml	While serum 25(OH)D and calcium levels increased in the treatment group, the iPTH, ALP, BAP, and CTX-1 levels decreased. However, no significant changes were observed in serum inorganic phosphate and iFGF-23 levels	[73]
Oral Cholecalciferol	300.000IU Once both at baseline and at 8 weeks	3 and 4	18-70 years old, non-diabetic subjects (n=120) 16 weeks	<20 ng/ml	While serum 25(OH)D and 1,25(OH)2D levels increased in the treatment group, the serum iPTH and ALP levels decreased significantly. Additionally, serum sclerostin levels did not change in the treatment group but decreased significantly in the placebo group.	[19]
Oral Cholecalciferol	50.000IU/week for 12 weeks followed by 50.000 IU every other week for 40 weeks	2 and 3	18-90 years old, individuals with CKD (n=37) 52 weeks	<30 ng/ml	Serum 25(OH)D levels increased in the treatment group at the end of 1 year of the study. Although the PTH level decreased significantly at the end of the 12 weeks of the study, this decrease was not significant compared to the placebo group at the end of 1 year of the study	[75]
Oral Cholecalciferol	8.000 IU once a day	3 and 4	18-85 years old, individuals with CKD (n=95) 12 weeks	<30ng/ml	Levels of 25 (OH) D and 1, 25 (OH)2D increased in the treatment group. While PTH levels increased in the placebo group, they remained stable in the treatment group. Serum calcium and phosphate levels did not differ between the groups	[76]
Oral Ergocalciferol	50.000 IU once a week	4 and 5	>18 years old, outpatients with CKD (n=43) 6 weeks	<30 ng/ml	Although plasma 25(OH)D2 levels increased in the treatment group, 1.25(OH)2D levels remained constant. In addition, no significant changes were observed in the serum phosphate, ionized calcium, PTH, and FGF-23 levels	[90]
Oral ER Calcifediol	30 µg once a day for 12 weeks followed by an additional 14 weeks of treatment with either 30 or 60 µg	3 and 4	≥ 18 years old, SHPT patients with CKD (n=354) 26 weeks	<20ng/ml	While serum 25(OH)D levels increased in the treatment group, the iPTH levels decreased significantly. Additionally, a slightly greater increase in the serum phosphorus and calcium levels was observed. However, there was no significant change in FGF-23 levels in the treatment group compared with the placebo group	[74]

* iPTH: Intact parathyroid hormone; ALP: Alkaline phosphatase; BSAP: Bone specific alkaline phosphatase; CTX-1: C-terminal telopeptide of type 1 collagen; iFGF-23: Intact fibroblast growth factor-23; PTH: Parathyroid hormone;

Table 4

Vitamin D treatment and several biochemical markers for the clinical assessment of osteoporosis in patients with CKD receiving dialysis treatment

Supplement Type	Dose	Participants and Study Duration	Vitamin D Level	Results	Reference
Oral Cholecalciferol	3.000IU thrice a week in group 1 9.000IU once a month in group 2	67 years old (median), Hemodialysis patients (n=88) 6 months	<15 ng/ml	The 25(OH)D levels were significantly increased in the treatment groups. Cholecalciferol further reduced iPTH levels in patients with 25(OH)D level of < 8ng/ml at 3 months. At the end of the study, there were no significant differences in serum calcium, phosphate, iPTH, and BSAP levels compared with the placebo group	[82]
Oral Cholecalciferol	10.000IU once a week	33-80 years old, Hemodialysis patients (n=42) 15 weeks	<20 ng/ml	The levels of 25(OH)D and 1,25(OH)2D levels were significantly increased in the treatment group. However, no significant difference was observed in serum calcium, phosphorus and PTH levels between the placebo and the treatment group	[91]
Oral Ergocalciferol	50.000 IU once a week in group 1 50.000 IU once a month in group 2	≥18 years old, Hemodialysis patients (n=105) 12 weeks	<32 ng/ml	The levels of serum 25(OH)D levels were increased in both treatment groups. However, no significant differences were observed between the groups in serum calcium, phosphate and PTH levels	[92]
Oral Cholecalciferol	3.000 IU/day	≥18 years old, Dialysis patients (n=50) 6 months	<32 ng/ml	Serum 25(OH)D levels increased in the treatment group. However, there was no significant difference in serum calcium, phosphate, PTH and ALP levels compared with the placebo group	[83]
Oral Cholecalciferol	4.800 IU/day	>17 years old, Peritoneal dialysis patients (n=58) 16 weeks	<20ng/ml	Serum iFGF-23, 25(OH)D and 1,25(OH)2D levels were significantly increased in the treatment group compared with the placebo group at the end of the study. However, no significant differences were observed between the groups in the levels of calcium, phosphorus, OPG, OCN, OPN and iPTH	[84]
Oral Cholecalciferol	50.000 IU/week	18-70 years old, Hemodialysis patients (n=86) 12 weeks	<30 ng/ml	The 25(OH)D and -klotho levels were significantly increased in the treatment group compared with the placebo group. Although serum FGF-23 levels decreased in the treatment group, the before-after differences were not significantly different from the placebo group	[93]
Oral Ergocalciferol	50.000 IU/week for 3 months followed by 50.000 IU/month 50.000 IU/week in severe deficiency	≥18 years old, Hemodialysis patients (n=276) 6 months	<30 ng/ml	Serum 25(OH)D levels was significantly increased in the treatment group compared with the placebo group. However, no significant differences were observed in serum calcium, phosphate and iPTH levels	[94]

* PTH: Parathyroid hormone; iPTH: Intact parathyroid hormone; ALP: Alkaline phosphatase; CTX-1: C-terminal telopeptide of type 1 collagen; FGF-23: Fibroblast growth factor-23; iFGF-23: Intact fibroblast growth factor-23; BSAP: Bone specific alkaline phosphatase; OPG: Osteoprotegerin; OCN: Osteocalcin; OPN: Osteopontin

Vitamin D supplementation is performed in the native form (ergocalciferol, cholecalciferol, and calcifediol) or with calcitriol and its analogs, active forms of vitamin D. The KDIGO guidelines do not recommend the routine use of calcitriol or vitamin D analogs in pre-dialysis patients but reserve them for the treatment of severe and progressive SHPT to prevent hypercalcemia and vascular calcification [42]. Owing to the possibility of extrarenal conversion of calcidiol to calcitriol, native vitamin D treatment has received increasing attention in the current literature as an alternative to calcitriol use in patients with CKD. Our findings from the current studies indicated that cholecalciferol and ergocalciferol treatment increased serum calcidiol levels in patients with stage 3-5 CKD. The findings also indicated that cholecalciferol treatment, but not ergocalciferol, has the potential to significantly increase serum calcitriol levels. Hypercalcemia, hyperphosphatemia, and kidney stones are of the greatest concern regarding high serum vitamin D levels. However, the current studies have reported that both cholecalciferol and ergocalciferol do not significantly increase serum calcium and phosphorus levels. Several meta-analyses have already reported that native vitamin D supplements do not increase serum calcium or phosphorus levels [70, 71].

Monitoring of serum iPTH levels from stage G3a in patients with CKD is recommended. Serum iPTH levels have been associated with renal and cardiovascular outcomes and even increased mortality [42]. K/DOQI guidelines have recommended correction of plasma calcidiol level on a 6-month regimen with ergocalciferol to treat increased PTH levels in patients with Stage 3-4 CKD [72]. Recent studies have shown that cholecalciferol and ergocalciferol do not significantly reduce or prevent the increase in iPTH levels in patients with CKD receiving dialysis treatment. This may be due to the small sample size and very high PTH levels in the patients.

There is limited evidence for the reduction of iPTH levels using native vitamin D treatment in pre-dialysis CKD patients. Yadav et al. (2018b) reported that 300,000 IU of oral cholecalciferol treatment, once at the start and at 8th week of the study, can effectively reduce iPTH levels in patients with stage 3-4 non-diabetic CKD [73]. Similarly, Sprague et al. (2016) reported that daily 30 and 60 µg ER calcifediol treatment significantly reduced iPTH levels in CKD patients with SHPT [74]. In this review, it is noteworthy that native vitamin D treatment was more effective in reducing iPTH levels in pre-dialysis CKD patients in studies where the sample size was large and participants with serum calcidiol levels <20 ng/ml were included in the study [73, 74]. Although some authors have reported that native vitamin D treatment is not effective in reducing PTH levels in predialysis CKD patients, most studies have demonstrated that it is at least effective in preventing further increases in PTH levels [75, 76].

The current KDIGO guidelines recommend the use of calcitriol and its analogs for stage 4-5 CKD pa-

tients with severe and progressive SHPT [42]. However, the concerns remain that calcitriol and its analogs may increase serum calcium and phosphorus levels [77, 78]. In particular, hypercalcemia may be associated with accelerated progression of cardiovascular calcification and worsening of renal function [42]. To our knowledge, only one study has reported a significantly higher incidence of hypercalcemia with calcitriol treatment than in the control group [79]. Moreover, calcitriol and paricalcitol treatment had a low stimulatory effect on serum calcium levels while being effective in suppressing iPTH levels [77, 80, 81]. A meta-analysis conducted by Christodoulou et al. (2021) showed that vitamin D treatment had an inconsistent effect on PTH concentrations, whereas treatment with calcifediol, calcitriol, and paricalcitol consistently reduced PTH [70].

The use of bone turnover biomarkers in clinical trials makes an important contribution to the understanding of the role of vitamin D in the treatment of osteoporosis and in predicting fracture risks. However, there are only 6 randomized controlled studies (comparator groups excluded) reporting the relationship between vitamin D treatment and bone turnover markers in patients with CKD. Recent studies have reported that cholecalciferol treatment (regardless of daily, weekly, or monthly use) has no significant effect on osteoporosis markers such as serum ALP, BSAP, osteoprotegerin, osteopontin, and osteocalcin in CKD patients receiving dialysis treatment [82-84]. In contrast, Wang et al. (2014) demonstrated that 1 µg/day oral paricalcitol treatment significantly reduced serum ALP levels after 52 weeks in stage 3-5 CKD patients with left ventricular hypertrophy compared to the placebo group [81]. Similarly, Yadav et al. (2018a) reported that 300,000 IU of oral cholecalciferol at the beginning and 8th week of the study increased serum ALP, BSAP, and C-terminal telopeptide of type 1 collagen (CTX-1) levels in non-diabetic patients with stage 3-4 CKD [19]. However, the authors added that the serum sclerostin levels in the treatment group were not significantly different from those in the placebo group.

It is well known that as renal function decreases in patients with CKD, FGF-23 secretion from osteoblasts and osteocytes increases [85]. Increased secretion of FGF-23 is hypothesized to occur during the early stages of CKD as a protective response to phosphate accumulation in the body. FGF23, with a co-receptor (Klotho protein), is a phosphaturic hormone that is predominantly produced by osteocytes. The cofactor α -klotho, whose expression decreases with aging and kidney dysfunction, decreases FGF23 receptor activation [86]. Therefore, increased FGF-23 in patients with CKD decelerates calcitriol synthesis by inhibiting CYP27B1, as well as decreasing renal phosphate reabsorption [23, 25]. Increased plasma FGF-23 concentration is associated with soft tissue calcification and the promotion of CKD-MBD [86]. The studies included in this review reported that native vitamin D treatment did not increase circular FGF-23 levels in patients with CKD.

Similarly, a recent meta-analysis of clinical trials reported that vitamin D treatment had no significant effect on plasma FGF-23 levels [87].

KDIGO recommends BMD measurement to decide treatment, especially in patients with stage 3-5D CKD, in the presence of CKD-MBD indicators and osteoporosis risk factors [42]. Therefore, findings on the effects of vitamin D treatment on BMD in patients with CKD are scarce. The findings from the DECALYOS II study highlighted that daily combined calcium (1200 mg) and cholecalciferol (800 IU) treatment was significantly effective in reducing BMD loss in vitamin D-deficient women with moderate CKD [88]. Additionally, Tsujita et al. (2022) evaluated changes in BMD in response to daily cholecalciferol in kidney transplant recipients with a mean serum 25(OH)D level of 10 ng/mL. Daily supplementation with 4000 IU of cholecalciferol for 12 months significantly increased lumbar spine BMD in kidney transplant recipients with osteoporosis/osteopenia, but not in those with normal BMD [89]. However, the findings of these studies are insufficient to provide evidence for the effect of vitamin D supplementation on BMD.

Conclusions. Inadequate circular vitamin D levels are observed in patients with CKD, which increase the risk of SHPT and bone fractures. Current international guidelines recommend vitamin D treatment in chronic kidney disease as in the general population. The current findings have reported that native vitamin D treatment, such as cholecalciferol and calcifediol, improves biochemical markers such as ALP, BSAP, and iPTH used for clinical assessment of osteoporosis in pre-dialysis CKD patients with a serum vitamin D level of <20 ng/ml. However, neither cholecalciferol nor ergocalciferol (regardless of daily, weekly, or monthly use) improved these biochemical markers in CKD patients receiving dialysis. The current KDIGO guidelines recommend the use of calcitriol and its analogs in stage 4-5 CKD patients with severe and progressive SHPT. However, the concerns remain that active vitamin D treatment may increase serum calcium and phosphorus levels. Hypercalcemia may be associated with the accelerated progression of cardiovascular calcification and worsen-

ing of renal function. The KDIGO guidelines do not recommend calcitriol and its analogs for CKD patients with hypercalcemia and hyperphosphatemia. In contrast, current findings have shown that both cholecalciferol and ergocalciferol do not significantly increase serum calcium and phosphorus levels in patients with CKD. Furthermore, some researchers have reported promising findings regarding ER calcifediol treatment for hypercalcemia and hyperphosphatemia.

Supplementation with native vitamin D has corrected vitamin D deficiency in CKD patients regardless of whether they are receiving dialysis treatment. Having adequate serum levels of 25(OH)D, which is greater than 30 ng/mL, is essential for preventing falls and fractures. Therefore, it is important to avoid vitamin D insufficiency and deficiency in CKD patients. Native vitamin D may also improve serum iPTH and bone biomarkers in the early stages of CKD. Despite limited evidence, it may be effective in reducing bone mineral density loss in CKD patients. Moreover, vitamin D has been shown to have several protective effects in CKD patients, such as improving proteinuria and renal function progression. Clinicians should therefore prescribe native vitamin D for bone health to CKD patients with vitamin D deficiency. However, the effectiveness of native vitamin D treatments on the progression of renal damage and fracture risk needs to be supported by more comprehensive studies.

Funding. The authors did not receive support from any organization for the submitted work.

Conflict of Interest. The authors declare that they have no conflicts of interest.

Ethics Approval. Authors declare that the article is original and not submitted anywhere else and the table and figure included in the article are original.

Data Availability. The data that support the findings of this study are available from the corresponding author.

Authors' Contributions.

S. Demirel: conceptualization, writing, drawing.

M. Gürbüz: conceptualization, writing, editing and supervision. All authors have read and approved the final manuscript.

References:

1. *Ammirati AL.* Chronic kidney disease. *Rev Assoc Med Bras* (1992). 2020 Jan 13;66Suppl 1(Suppl 1):s03-s09. doi:10.1590/1806-9282.66.S1.3.
2. *Levin A, Tonelli M, Bonventre J, Coresh J, Donner J-A, Fogo AB, et al.* Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet*. 2017 Oct 21;390(10105):1888-917. doi:10.1016/s0140-6736(17)30788-2.
3. *Süleymanlar G, Utaş C, Arinsoy T, Ateş K, Altun B, Altıparmak MR et al.* A population-based survey of Chronic REnal Disease In Turkey - the CREDIT study. *Nephrol Dial Transplant*. 2011 Jun;26(6):1862-71. doi:10.1093/ndt/gfq656.
4. *Swartling O, Rydell H, Stendahl M, Segelmark M, Trolle Lagerros Y, Evans M.* CKD progression and mortality among men and women: A nationwide study in Sweden. *Am J Kidney Dis*. 2021 Aug;78(2):190-9.e1. doi: 10.1053/j.ajkd.2020.11.026.
5. *Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al.* Global prevalence of chronic kidney disease – A systematic review and meta-analysis. *Plos One*. 2016 Jul 6;11(7):e0158765. doi: 10.1371/journal.pone.0158765.
6. *Luyckx VA, Tonelli M, Stanifer JW.* The global burden of kidney disease and the sustainable develop-

- ment goals. *Bull World Health Organ.* 2018 Jun 1;96(6):414-22d. doi: 10.2471/blt.17.206441.
7. *Yiğit V.* Türkiye’de diyaliz ve böbrek transplantasyonu tedavisinin maliyet etkililik analizi. Mehmet Akif Ersoy Üniversitesi Sosyal Bilimler Enstitüsü Dergisi. [Internet]. 2015 Nov 1;1(13):182-205. Available from: <https://dergipark.org.tr/tr/download/article-file/181877>.
 8. *Korkmaz ÖP, Kadioğlu P.* Kronik böbrek hastalığında osteoporoz ve tedavisi. *Türkiye Klinikleri J Nephrol.* 2018;11(1):75-80.
 9. *Hampson G, Elder GJ, Cohen-Solal M, Abrahamson B.* A review and perspective on the assessment, management and prevention of fragility fractures in patients with osteoporosis and chronic kidney disease. *Endocrine.* 2021 Sep;73(3):509-29. doi: 10.1007/s12020-021-02735-9.
 10. *Casado E, Bover J, Gómez-Alonso C, Navarro-González JF.* Osteoporosis in chronic kidney disease: A essential challenge. *Med Clin (English Edition).* 2022 Jan 7;158(1):27-34. doi: 10.1016/j.medcli.2021.05.007.
 11. *Wu CC, Liao MT, Hsiao PJ, Lu CL, Hsu YJ, Lu KJ, et al.* Antiproteinuria effect of calcitriol in patients with chronic kidney disease and vitamin d deficiency: a randomized controlled study. *J Ren Nutr.* 2020 May;30(3):200-7. doi: 10.1053/j.jrn.2019.09.001.
 12. *Zappulo F, Cappuccilli M, Cingolani A, Scrivo A, Chiochini AL, Nunzio MD, et al.* Vitamin D and the kidney: two players, one console. *Int J Mol Sci.* 2022 Aug 15;23(16):9135. doi: 10.3390/ijms23169135.
 13. *Keung L, Perwad F.* Vitamin D and kidney disease. *Bone Rep.* 2018 Dec 1;9:93-100. doi: 10.1016/j.bonr.2018.07.002.
 14. *Shen Q, Bi X, Ling L, Ding W.* 1,25-Dihydroxyvitamin D3 attenuates angiotensin ii-induced renal injury by inhibiting mitochondrial dysfunction and autophagy. *Cell Physiol Biochem.* 2018 Nov 30;51(4):1751-62. doi: 10.1159/000495678.
 15. *Williams S, Malatesta K, Norris K.* Vitamin D and chronic kidney disease. *Ethn Dis.* [Internet]. 2009 Autumn;19(4 Suppl 5):S5-8-11. Available from: <https://pubmed.ncbi.nlm.nih.gov/20077598/>.
 16. *Liu C, Li H.* Correlation of the severity of chronic kidney disease with serum inflammation, osteoporosis and vitamin D deficiency. *Exp Ther Med.* 2019 Jan; 17(1):368-72. doi: 10.3892/etm.2018.6916.
 17. *Jhee JH, Nam KH, An SY, Cha MU, Lee M, Park S, et al.* Severe vitamin D deficiency is a risk factor for renal hyperfiltration. *Am J Clin Nutr.* 2018 Dec 1;108(6):1342-51. doi: 10.1093/ajcn/nqy194.
 18. *Goto NA, Weststrate ACG, Oosterlaan FM, Verhaar MC, Willems HC, Emmelot-Vonk MH, et al.* The association between chronic kidney disease, falls, and fractures: a systematic review and meta-analysis. *Osteoporosis Int.* 2020 Jan;31(1):13-29. doi: 10.1007/s00198-019-05190-5.
 19. *Yadav AK, Kumar V, Kumar V, Banerjee D, Gupta KL, Jha V.* The effect of vitamin d supplementation on bone metabolic markers in chronic kidney disease. *J Bone Miner Res.* 2018 Mar;33(3):404-9. doi: 10.1002/jbmr.3314.
 20. *Kruger MC, Chan YM, Lau LT, Lau CC, Chin YS, Kuhn-Sherlock B, et al.* Calcium and vitamin D fortified milk reduces bone turnover and improves bone density in postmenopausal women over 1 year. *Eur J Nutr.* 2018 Dec;57(8):2785-94. doi: 10.1007/s00394-017-1544-6.
 21. *Saponaro F, Saba A, Zucchi R.* An update on vitamin D metabolism. *Int J Mol Sci.* 2020 Sep 8;21(18):6573. doi: 10.3390/ijms21186573.
 22. *Negrea L.* Active vitamin D in chronic kidney disease: Getting Right Back Where We Started from? *Kidney Dis.* 2019 Mar;5(2):59-68. doi: 10.1159/000495138.
 23. *Christakos S, Li S, De La Cruz J, Bikle DD.* New developments in our understanding of vitamin D metabolism, action and treatment. *Metabolism.* 2019 Sep 1;98:112-20. doi: 10.1016/j.metabol.2019.06.010.
 24. *Rayego-Mateos S, Dolad N, Garcia-Carrasco A, Diaz-Tocados JM, Ibarz M, Valdivielso JM.* The increase in FGF23 induced by calcium is partially dependent on vitamin D signaling. *Nutrients.* 2022 Jun 22;14(13):2576. doi: 10.3390/nu14132576.
 25. *Erben RG.* Physiological actions of fibroblast growth factor-23. *Front Endocrinol (Lausanne).* 2018 May 28;9:267. doi: 10.3389/fendo.2018.00267.
 26. *Lips P, Eekhoff M, van Schoor N, Oosterwerff M, de Jong R, Krul-Poel Y, et al.* Vitamin D and type 2 diabetes. *J Steroid Biochem Mol Biol.* 2017 Oct;173:280-5. doi: 10.1016/j.jsbmb.2016.11.021.
 27. *Hong HH, Hong A, Wang CC, Huang EW, Chiang CC, Yen TH, et al.* Calcitriol exerts a mineralization-inductive effect comparable to that of vitamin C in cultured human periodontium cells. *Am J Transl Res.* [Internet]. 2019 Apr 15;11(4):2304-2316. Available from: <https://pubmed.ncbi.nlm.nih.gov/31105837/>.
 28. *Liu H, Cui J, Feng W, Lv S, Du J, Sun J, et al.* Local administration of calcitriol positively influences bone remodeling and maturation during restoration of mandibular bone defects in rats. *Mater Sci Eng C Mater Biol Appl.* 2015 Apr;49:14-24. doi: 10.1016/j.msec.2014.12.064.
 29. *Capelli I, Cianciolo G, Gasperoni L, Galassi A, Ciceri P, Cozzolino M.* Nutritional vitamin D in CKD: Should we measure? Should we treat? *Clin Chim Acta.* 2020 Feb;501:186-97. doi: 10.1016/j.cca.2019.11.010.
 30. *Atkins GJ, Anderson PH, Findlay DM, Welldon KJ, Vincent C, Zennettino AC, et al.* Metabolism of vitamin D3 in human osteoblasts: evidence for autocrine and paracrine activities of 1 alpha,25-dihy-

- droxyvitamin D3. *Bone*. 2007 Jun;40(6):1517-28. doi: 10.1016/j.bone.2007.02.024.
31. *Bover J, Egado J, Fernández-Giráldez E, Praga M, Solozabal-Campos C, Torregrosa JV, et al.* Vitamin D, vitamin D receptor and the importance of its activation in patients with chronic kidney disease. *Nefrologia (English Edition)*. 2015 Jan;35(1):28-41. doi: 10.3265/Nefrologia.pre2014.Sep.11796.
 32. *Brandenburg V, Ketteler M.* Vitamin D and secondary hyperparathyroidism in chronic kidney disease: a critical appraisal of the past, present, and the future. *Nutrients*. 2022 Jul 22;14(15):3009. doi: 10.3390/nu14153009.
 33. *Lu CL, Yeih DF, Hou YC, Jow GM, Li ZY, Liu WC, et al.* The emerging role of nutritional vitamin d in secondary hyperparathyroidism in CKD. *Nutrients*. 2018 Dec 3;10(12):1890. doi: 10.3390/nu10121890.
 34. *Chen TK, Knicely DH, Grams ME.* Chronic kidney disease diagnosis and management. *JAMA*. 2019 Oct 1;322(13):1294. doi: 10.1001/jama.2019.14745.
 35. *Lee SW, Russell J, Avioli LV.* 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol: conversion impaired by systemic metabolic acidosis. *Science*. 1977 Mar 11;195(4282):994-6. doi: 10.1126/science.841324.
 36. *Cashman KD, Van Den Heuvel EG, Schoemaker RJ, Prévéraud DP, Macdonald HM, Arcot J.* 25-Hydroxyvitamin D as a biomarker of vitamin d status and its modeling to inform strategies for prevention of vitamin d deficiency within the population. *Adv Nutr*. 2017 Nov 15;8(6):947-57. doi: 10.3945/an.117.015578.
 37. *Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Berisha AT, et al.* Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr*. 2020 Nov;74(11):1498-1513. doi: 10.1038/s41430-020-0558-y.
 38. *Park J, Ryu S-Y, Han M-A, Choi S-W.* The association of vitamin D with estimated glomerular filtration rate and albuminuria: 5th Korean National Health and Nutritional Examination Survey 2011-2012. *J Ren Nutr*. 2016 Nov;26(6):360-6. doi: 10.1053/j.jrn.2016.07.003.
 39. *Niculescu DA, Deacu LG, Caragheorghopol A, Popescu N, Ghemigian A, Procopiuc C, et al.* Combined effects of vitamin D status, renal function and age on serum parathyroid hormone levels. *Front Endocrinol*. 2021 Apr 30;12:657991. doi: 10.3389/fendo.2021.657991.
 40. *Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al.* Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int*. 2007 Oct;72(8):1004-13. doi: 10.1038/sj.ki.5002451.
 41. *Feehan O, Armstrong D, Magee P, Pourshahidi KL, Strain JJ, Beggan L, et al.* Vitamin D and bone health of older adults within care homes: An observational study. *Nutrients*. 2022 Jun 28;14(13):2680. doi: 10.3390/nu14132680.
 42. *Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group.* KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2017 Jul;7(1):1-59. doi: 10.1016/j.kisu.2017.04.001.
 43. *Hsu C-Y, Chen L-R, Chen K-H.* Osteoporosis in patients with chronic kidney diseases: a systemic review. *Int J Mol Sci*. 2020 Sep 18;21(18):6846. doi: 10.3390/ijms21186846.
 44. *Bellorin-Font E, Rojas E, Martin KJ.* Bone Disease in chronic kidney disease and kidney transplant. *Nutrients*. 2023 Dec 29;15(1):167. doi: 10.3390/nu15010167.
 45. *Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al.* Definition, evaluation, and classification of renal osteodystrophy: a position statement from kidney disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2006 Jun;69(11):1945-53. doi: 10.1038/sj.ki.5000414.
 46. *Hall RK, Sloane R, Pieper C, van Houtven C, LaFleur J, Adler R, et al.* Competing risks of fracture and death in older adults with chronic kidney disease. *J Am Geriatr Soc*. 2018 Mar;66(3):532-538. doi: 10.1111/jgs.15256.
 47. *Torres PAU, Cohen-Solal M.* Evaluation of fracture risk in chronic kidney disease. *J Nephrol*. 2017 Oct;30(5):653-61. doi: 10.1007/s40620-017-0398-6.
 48. *Khairallah P, Nickolas TL.* Updates in CKD-associated osteoporosis. *Curr Osteoporos Rep*. 2018 Dec;16(6):712-23. doi: 10.1007/s11914-018-0491-3.
 49. *Gómez-Islas VE, García-Fong KR, Aguilar-Fuentes RE, Hernández-Castellanos S, Pherez-Farah A, Méndez-Bribiesca SA, et al.* Evaluation of bone densitometry by dual-energy x-ray absorptiometry as a fracture prediction tool in women with chronic kidney disease. *Bone Rep*. 2020 Dec;13:100298. doi: 10.1016/j.bonr.2020.100298.
 50. *West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D, et al.* Retracted: bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res*. 2015 May;30(5):913-919. doi: 10.1002/jbmr.2406.
 51. *Klawansky S, Komaroff E, Cavanaugh PF, Mitchell DY, Gordon MJ, Connelly JE, et al.* Relationship between age, renal function and bone mineral density in the US population. *Osteoporos Int*. 2003 Jul;14(7):570-6. doi: 10.1007/s00198-003-1435-y.
 52. *Nickolas TL, McMahon DJ, Shane E.* Relationship between moderate to severe kidney disease and

- hip fracture in the United States. *J Am Soc Nephrol*. 2006 Nov;17(11):3223-32. doi: 10.1681/asn.2005111194.
53. *Miller PD*. Chronic kidney disease and osteoporosis: evaluation and management. *Bonekey Rep*. 2014 Jun 25;3:542. doi: 10.1038/bonekey.2014.37.
54. *Hsu C-Y, Cummings SR, McCulloch CE, Chertow GM*. Bone mineral density is not diminished by mild to moderate chronic renal insufficiency. *Kidney Int*. 2002 May;61(5):1814-20. doi: 10.1046/j.1523-1755.2002.00306.x.
55. *Kuipers AL, Egwuogu H, Evans RW, Patrick AL, Youk A, Bunker CH, et al*. Renal function and bone loss in a cohort of Afro-Caribbean men. *J Bone Miner Res*. 2015 Dec;30(12):2215-20. doi: 10.1002/jbmr.2562.
56. *Tasnim N, Dutta P, Nayeem J, Masud P, Ferdousi A, Ghosh AS, et al*. Osteoporosis, an inevitable circumstance of chronic kidney disease: A systematic review. *Cureus*. 2021 Oct 5;13(10):e18488. doi: 10.7759/cureus.18488.
57. *Orlic L, Crncevic Z, Pavlovic D, Zaputovic L*. Bone mineral densitometry in patients on hemodialysis: difference between genders and what to measure. *Ren Fail*. 2010;32(3):300-8. doi: 10.3109/08860221003611661.
58. *Tariq MH, Sulaiman SA*. Prevalence of osteopenia and osteoporosis among chronic kidney disease patients: A systematic review. *Open Urol Nephrol J*. 2020 May 23;13(1):5-12. doi: 10.2174/1874303x02013010005.
59. *Yucel Kocak S, Ozdemir A*. Comparison of bone mineral density and biochemical factors in hemodialysis and peritoneal dialysis patients. *Clin Nephrol*. 2022 Sep;98(3):115-22. doi: 10.5414/cn110729.
60. *Nazzal Z, Khader S, Zawyani H, Abdallah M, Sawalmeh O, Hamdan Z*. Bone mineral density in Palestinian patients with end-stage renal disease and the related clinical and biochemical factors: Cross-sectional study. *Plos One*. 2020 Nov 12;15(11):e0241201. doi: 10.1371/journal.pone.0241201.
61. *Lv J, Xie W, Wang S, Zhu Y, Wang Y, Zhang P, et al*. Associated factors of osteoporosis and vascular calcification in patients awaiting kidney transplantation. *Int Urol Nephrol*. 2023 Apr 24;55:3217-24. doi: 10.1007/s11255-023-03606-0.
62. *Cardwell G, Bornman J, James A, Black L*. A review of mushrooms as a potential source of dietary vitamin D. *Nutrients*. 2018 Oct 13;10(10):1498. doi: 10.3390/nu10101498.
63. *Ziemińska M, Sieklucka B, Pawlak K*. Vitamin K and D supplementation and bone health in chronic kidney disease—apart or together? *Nutrients*. 2021 Mar 1;13(3):809. doi: 10.3390/nu13030809.
64. *Dominguez LJ, Farruggia M, Veronese N, Barbagallo M*. Vitamin D sources, metabolism, and deficiency: available compounds and guidelines for its treatment. *Metabolites*. 2021 Apr;11(4):255. doi: 10.3390/metabo11040255.
65. *de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H*. Vitamin D and cardiovascular health. *Clin Nutr*. 2021 May;40(5):2946-57. doi: 10.1016/j.clnu.2020.12.025.
66. U.S. Department of Agriculture, Agricultural Research Service. FoodData Central. [Internet] 2019. Available from: fdc.nal.usda.gov.
67. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Dietary reference values for vitamin D. *EFSA Journal*. 2016 Oct 28;14(10):e04547. doi: 10.2903/j.efsa.2016.4547.
68. *Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, Leboff MS, et al*. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int*. 2016 Jan;27(1):367-76. doi: 10.1007/s00198-015-3386-5.
69. *Carmel AS, Shieh A, Bang H, Bockman RS*. The 25(OH)D level needed to maintain a favorable bisphosphonate response is ≥ 33 ng/ml. *Osteoporos Int*. 2012 Oct;23(10):2479-87. doi: 10.1007/s00198-011-1868-7.
70. *Christodoulou M, Aspray TJ, Schoenmakers I*. Vitamin D supplementation for patients with chronic kidney disease: A systematic review and meta-analyses of trials investigating the response to supplementation and an overview of guidelines. *Calcif Tissue Int*. 2021 Aug;109(2):157-78. doi: 10.1007/s00223-021-00844-1.
71. *Bover J, Ureña-Torres P, Laiz Alonso AM, Torregrosa JV, Rodríguez-García M, Castro-Alonso C, et al*. Osteoporosis, bone mineral density and CKD-MBD (II): Therapeutic implications. *Nefrologia (Engl Ed)*. 2019 May-Jun;39(3):227-42. doi: 10.1016/j.nefro.2018.10.009.
72. *Eknayan G, Levin A, Levin NW*. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003 Oct;42(4 Suppl 3):S1-201. doi: 10.1016/s0272-6386(03)00905-3.
73. *Yadav AK, Kumar V, Banerjee D, Gupta KL, Jha V*. Effect of vitamin D supplementation on serum sclerostin levels in chronic kidney disease. *J Steroid Biochem Mol Biol*. 2018 Jun;180:15-18. doi:10.1016/j.jsbmb.2018.01.007.
74. *Sprague SM, Crawford PW, Melnick JZ, Strugnell SA, Ali S, Mangoo-Karim R, et al*. Use of extended-release calcifediol to treat secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. *Am J Nephrol*. 2016 Sep 28;44(4):316-25. doi: 10.1159/000450766.
75. *Alvarez JA, Law J, Coakley KE, Zughaier SM, Hao Li, Salles KS, et al*. High-dose cholecalcif-

- erol reduces parathyroid hormone in patients with early chronic kidney disease: a pilot, randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr.* 2012 Sep;96(3):672-9. doi: 10.3945/ajcn.112.040642.
76. *Westerberg PA, Sterner G, Ljunggren Ö, Isaksson E, Elvarson F, Dezfoolian H, et al.* High doses of cholecalciferol alleviate the progression of hyperparathyroidism in patients with CKD Stages 3-4: results of a 12-week double-blind, randomized, controlled study. *Nephrol Dial Transplant.* 2018 Mar 1;33(3):466-71. doi: 10.1093/ndt/gfx059.
77. *Kendrick J, Andrews E, You Z, Moreau K, Nowak KL, Farmer-Bailey H, et al.* Cholecalciferol, calcitriol, and vascular function in CKD: A randomized, double-blind trial. *Clin J Am Soc Nephrol.* 2017 Sep 7;12(9):1438-46. doi: 10.2215/cjn.01870217.
78. *Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM.* A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3-4 CKD. *Clin J Am Soc Nephrol.* 2014 Sep 5;9(9):1620-6. doi: 10.2215/cjn.10661013.
79. *Prasad V, Cifu A.* Eliminating chronic kidney disease... as a diagnosis. *Pol Arch Med Wewn.* 2014;124(1-2):7-9. doi: 10.20452/pamw.2067.
80. *Wang AY-M, Fang F, Chan J, Wen YY, Qing S, Chan I-HS, et al.* Effect of paricalcitol on left ventricular mass and function in CKD—the OPERA trial. *J Am Soc Nephrol.* 2014 Jan;25(1):175-86. doi: 10.1681/ASN.2013010103.
81. *Kovesdy CP, Lu JL, Malakauskas SM, Andress DL, Kalantar-Zadeh K, Ahmadzadeh S.* Paricalcitol versus ergocalciferol for secondary hyperparathyroidism in CKD stages 3 and 4: a randomized controlled trial. *Am J Kidney Dis.* 2012 Jan;59(1):58-66. doi: 10.1053/j.ajkd.2011.06.027.
82. *Obi Y, Yamaguchi S, Hamano T, Sakaguchi Y, Shimomura A, Namba-Hamano T, et al.* Effect of cholecalciferol on serum hepcidin and parameters of anaemia and CKD-MBD among haemodialysis patients: a randomized clinical trial. *Sci Rep.* 2020 Sep 23;10(1):15500. doi: 10.1038/s41598-020-72385-w.
83. *Mose FH, Vase H, Larsen T, Kancir AS, Kosierkiewicz R, Jonczy B, et al.* Cardiovascular effects of cholecalciferol treatment in dialysis patients – a randomized controlled trial. *BMC Nephrol.* 2014 Mar 24;15(1):50. doi: 10.1186/1471-2369-15-50.
84. *Ramirez-Sandoval JC, Arvizu-Hernandez M, Cruz C, Vazquez-Cantu B, Rojas-Concha LJ, Tamez L, et al.* Cholecalciferol supplementation increases FGF23 in peritoneal dialysis patients with hypovitaminosis D: A randomized clinical trial. *J Nephrol.* 2019 Aug;32:645-59. doi: 10.1007/s40620-019-00599-x.
85. *Russo D, Battaglia Y.* Clinical significance of FGF-23 in patients with CKD. *Int J Nephrol.* 2011;2011:364890. doi: 10.4061/2011/364890.
86. *Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, et al.* Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int.* 2011 Jun;79(12):1370-78. doi: 10.1038/ki.2011.47.
87. *Karimi E, Bitarafan S, Mousavi SM, Zargarzadeh N, Mokhtari P, Hawkins J, et al.* The effect of vitamin D supplementation on fibroblast growth factor 23 in patients with chronic kidney disease: A systematic review and meta analysis. *Phytother Res.* 2021 Oct;35(10):5339-51. doi: 10.1002/ptr.7139.
88. *Bosworth C, de Boer IH.* Impaired vitamin D metabolism in CKD. *Semin Nephrol.* 2013 Mar;33(2):158-68. doi: 10.1016/j.semnephrol.2012.12.016.
89. *Tsujita M, Doi Y, Obi Y, Hamano T, Tomosugi T, Futamura K, et al.* Cholecalciferol supplementation attenuates bone loss in incident kidney transplant recipients: A prespecified secondary endpoint analysis of a randomized controlled trial. *J Bone Min Res.* 2022 Feb;37(2):303-11. doi: 10.1002/jbmr.4469.