



The relationship between vitamin D, chronic kidney disease, and mineral and bone disorder: a complex interplay comprehensive review

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Abstract

Chronic kidney disease (CKD) is a global health concern with a significant prevalence. One major complication of CKD is mineral and bone disorder (MBD), characterized by abnormalities in calcium, phosphate, and parathyroid hormone (PTH) levels, leading to bone mineral density loss and increased fracture risk. Vitamin D deficiency is highly prevalent in CKD patients due to impaired kidney function and reduced sun exposure. This deficiency further contributes to CKD-MBD pathogenesis. This review explores the complex interplay between Vitamin D, CKD, and MBD. We examine how CKD disrupts Vitamin D metabolism, leading to deficiency and its consequences for bone health and mineral homeostasis. We critically evaluate the current evidence on Vitamin D supplementation in CKD, focusing on its impact on bone mineral density (BMD), fracture risk, calcium, phosphate, and PTH levels. We discuss the limitations of existing research and highlight the need for further studies to establish definitive recommendations for Vitamin D management in CKD-MBD treatment strategies.

Key words CKD, MBD, Vit-D, PTH, metabolism, hypertension

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Introduction

Chronic kidney disease (CKD) is a progressive and irreversible condition characterized by a gradual decline in kidney function [1]. The kidneys are vital organs responsible for filtering waste products from the blood, regulating blood pressure, producing hormones, and maintaining electrolyte balance. In CKD, this filtration capacity deteriorates over time, leading to a buildup of toxins in the blood and a variety of health complications [1, 2].

CKD affects millions of people worldwide, with an estimated global prevalence of 8-16%, depending on the diagnostic criteria used [3]. This translates to hundreds of millions of individuals living with CKD. The risk of CKD increases with age, and it is a significant comorbidity in conditions like diabetes and hypertension [4]. The global burden of CKD is substantial, with associated healthcare costs exceeding \$1 trillion USD annually. Rising mortality rates highlight the seriousness of CKD, with cardiovascular disease being a major cause of death in CKD patients. Early diagnosis and management are crucial to slow disease progression and prevent complications [5].

Chronic Kidney Disease (CKD) is categorized into five stages based on the estimated glomerular filtration rate (eGFR), which indicates the kidneys' filtering ability. The stages are as follows:

Stage 1: Mild decrease in kidney function (eGFR 90-60 mL/min/1.73 m²);

Stage 2: Moderate decrease in kidney function (eGFR 59-30 mL/min/1.73 m²);

Stage 3: Moderate to severe decrease in kidney function (eGFR 29-15 mL/min/1.73 m²);

Stage 4: Severe decrease in kidney function (eGFR 14-9 mL/min/1.73 m²);

Stage 5: Kidney failure (eGFR <9 mL/min/1.73 m²) necessitating dialysis or kidney transplantation [6].

Impact of CKD on overall health and complications

CKD can significantly impact a person's overall health and well-being. As kidney function declines, various complications can arise, including:

- Cardiovascular Disease:** CKD patients are at increased risk for heart attack, stroke, and peripheral artery disease due to factors like hypertension, dyslipidemia, and inflammation [7].
- Bone and Mineral Disease:** Vitamin D deficiency and impaired calcium and phosphorus metabolism in CKD contribute to bone mineral density loss, increasing the risk of fractures and bone deformities.
- Anemia:** CKD disrupts the production of erythropoietin, a hormone essential for red blood cell production, leading to anemia and fatigue.
- Electrolyte Imbalances:** Impaired kidney function can cause imbalances in electrolytes like potassium, sodium, and calcium, leading to muscle cramps, weakness, and cardiac arrhythmias.
- Neuropathy:** Damage to peripheral nerves due to waste product buildup can cause pain, numbness, and weakness in the hands and feet. These complications can significantly reduce quality of life and increase healthcare utilization in CKD patients [7, 8].

Mineral and bone disorder in CKD

MBD is a significant complication of CKD, characterized by abnormalities in mineral and bone metabolism. It manifests as:

- Calcium and Phosphate Imbalances:** Disrupted kidney function in CKD leads to imbalances in calcium and phosphate levels in the blood. Low calcium levels can lead to secondary hyperparathyroidism, while elevated phosphate levels contribute to ectopic calcification in soft tissues, further compromising cardiovascular health.
- Secondary Hyperparathyroidism:** Chronic low calcium levels stimulate the parathyroid glands to produce

excess PTH. PTH mobilizes calcium from bones, leading to bone resorption and weakening [9]. This can cause bone pain, deformities, and increase the risk of fractures [10].

Skeletal Manifestations: Bone mineral density loss due to MBD increases the risk of fractures, especially hip and vertebral fractures, significantly impacting mobility and quality of life [11].

Extra-skeletal Manifestations: Elevated PTH levels and ectopic calcification can contribute to cardiovascular complications, vascular stiffness, and impaired vascular function [12]. This further increases the cardiovascular burden in CKD patients who are already at high risk.

The essential vitamin D

Vitamin D, often referred to as the "sunshine vitamin," plays a crucial role in maintaining bone health and mineral homeostasis. While it can be obtained from dietary sources like fatty fish and fortified foods, sunlight exposure remains the primary source for most individuals. Vitamin D undergoes a complex metabolic process to become biologically active [13].

Metabolism of vitamin D

The **Figure 1** represents the overview of Vit D synthesis, intake and activation:

Synthesis: Ultraviolet B (UVB) rays from sunlight penetrate the skin and trigger the production of vitamin D₃ (cholecalciferol) in the epidermis.

Hydroxylation: Vitamin D₃ is transported to the liver where it undergoes the first hydroxylation step by 25-hydroxylase, converting it to 25-hydroxyvitamin D (25(OH) D). This form serves as the major storage and circulation form of vitamin D in the body.

Activation: The final activation step occurs in the healthy kidneys. The enzyme 1-alpha-hydroxylase converts 25(OH) D into the biologically active form, 1, 25-dihydroxyvitamin D (1, 25(OH) 2D).

Physiological functions of vitamin D

1, 25 (OH) D acts through vitamin D receptors (VDRs) present in various tissues throughout the body. It exerts a wide range of physiological functions, including:

- Calcium Homeostasis:** Vitamin D promotes intestinal calcium absorption and facilitates calcium reabsorption in the kidneys, ensuring adequate calcium levels for bone mineralization [14].
- Bone Health:** Vitamin D directly stimulates osteoblast activity, promoting bone formation, and indirectly inhibits osteoclast activity, reducing bone resorption [15].
- Muscle Function:** Vitamin D receptors are present in skeletal muscle, and deficiency may contribute to muscle weakness and impaired physical function [16].
- Immune Function:** Vitamin D modulates the immune system, potentially influencing susceptibility to infections [17].

Disruption of vitamin D metabolism in CKD

CKD disrupts Vitamin D metabolism at several key points, leading to deficiency and contributing to MBD pathogenesis [18]:

- Decreased Kidney Function:** Healthy kidneys convert inactive Vitamin D (25(OH) D) to its active form, 1, 25(OH) 2D. However, in CKD, impaired 1-alpha-hydroxylase activity in the kidneys leads to a decline in 1, 25(OH) 2D production. This deficiency in the active form reduces the intestinal calcium absorption and bone mineralizing effects of Vitamin D [18].
- Reduced Sun Exposure:** Certain CKD patients with limited mobility or undergoing dialysis may have reduced sun exposure, a primary source of Vitamin

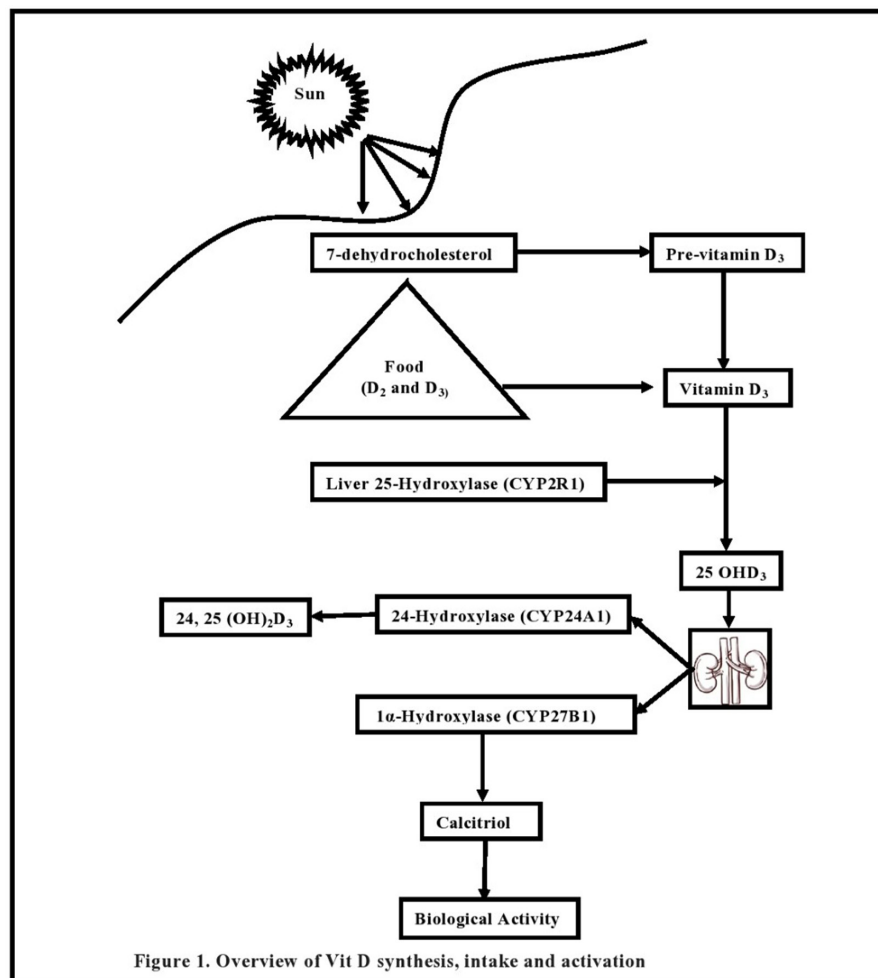


Figure 1. Flow chart of study participants evaluated for neck pain among smartphone users.

D synthesis. This can further exacerbate vitamin D deficiency [19]. Dietary Factors: Reduced dietary intake of Vitamin D-rich foods or impaired fat absorption due to CKD can contribute to deficiency. Additionally, medications used in CKD management may interact with Vitamin D metabolism [19].

Vitamin D deficiency and consequences in CKD-MBD

Vitamin D deficiency in CKD patients can exacerbate MBD by [18, 20]: Impaired Calcium Absorption: Reduced intestinal calcium absorption due to Vitamin D deficiency contributes to low calcium levels, hindering bone mineralization and promoting secondary hyperparathyroidism [18]. Secondary Hyperparathyroidism: Chronic low calcium levels stimulate PTH secretion from the parathyroid glands, leading to secondary hyperparathyroidism. This condition is associated with bone resorption, increased fracture risk, and ectopic calcification [20]. Muscle Weakness: Vitamin D deficiency may contribute to muscle weakness, further impacting bone health, functional abilities, and increasing the risk of falls and fractures. Immune Dysfunction: Vitamin D deficiency may impair immune function, potentially increasing susceptibility to infections in CKD patients with already compromised immune systems [17].

Clinical Implications of Vitamin D Supplementation in CKD-MBD

Vitamin D supplementation is a potential therapeutic strategy in CKD-MBD management. However, the current evidence regarding its efficacy and optimal dosing remains complex and requires further investigation. This section critically evaluates existing research on the impact of Vitamin D supplementation on various aspects of CKD-MBD.

Impact on bone health

Several studies have investigated the effect of Vitamin D supplementation on BMD in CKD patients. Here's a summary with key findings and limitations:

Randomized controlled trials (RCTs) by Theobald et al. (2010) [21] and Locatelli et al. (2002) [22] demonstrated improvements in BMD with supplementation compared to placebo. These studies suggest that Vitamin D may promote bone mineralization and potentially slow bone loss in CKD patients.

A meta-analysis by Mathieu et al. (2017) [23] found limited evidence for significant overall BMD improvements across various

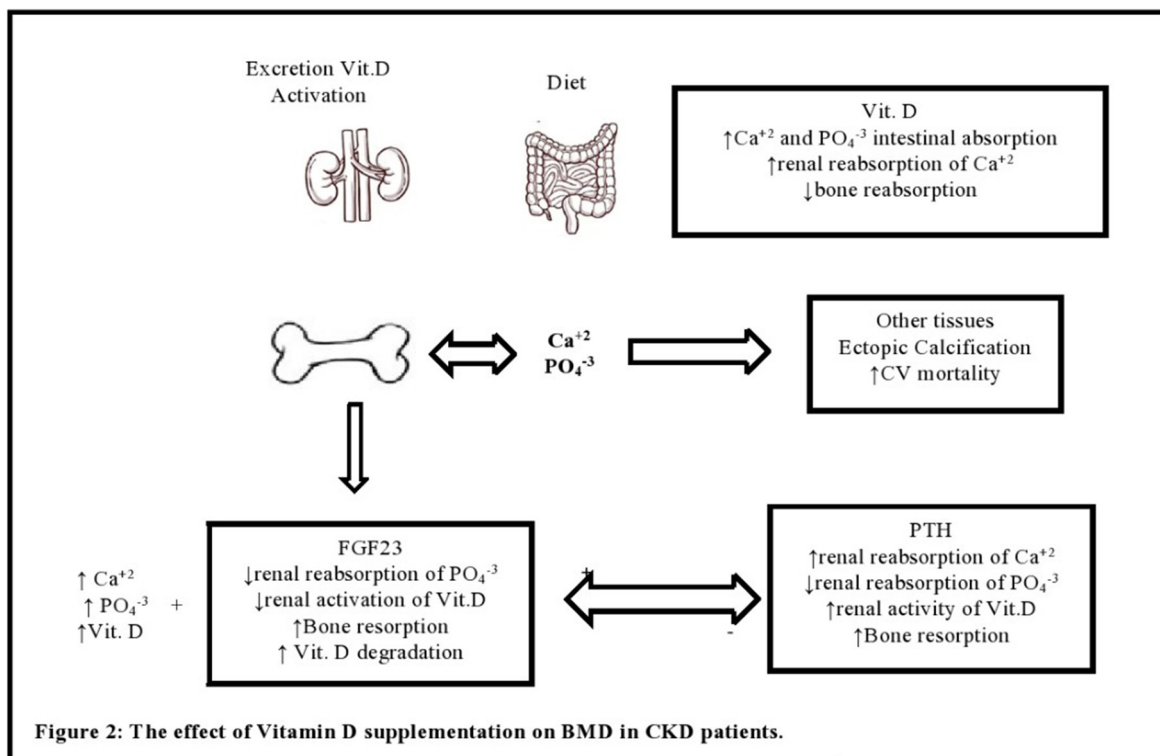


Figure 2. Prevalence of neck pain among smart phone users.

studies. Heterogeneity in study design (dosage, duration), baseline vitamin D levels, and patient populations contribute to these inconsistencies (Figure 2).

Larger, well-designed RCTs with standardized protocols and longer follow-up periods are needed to definitively assess the impact of Vitamin D supplementation on BMD in CKD populations.

The Observational studies suggest an association between Vitamin D deficiency and increased fracture risk in CKD patients [24]. However, RCTs haven't shown consistent benefits. Studies by Locatelli et al. (2002) [22] and Manolagas et al. (2008) [25] haven't consistently shown a reduction in fracture risk with Vitamin D supplementation in CKD patients. Reasons for inconsistent findings in RCTs may include insufficient sample size, follow-up duration, and variations in baseline fracture risk or medication use amongst participants [26]. Further research exploring optimal dosing strategies, combination therapies with other medications, and targeting specific patient subgroups at high fracture risk is warranted to elucidate the potential benefits of Vitamin D for fracture prevention in CKD [26].

Impact on mineral homeostasis

Vitamin D supplementation can increase serum calcium levels in CKD patients due to its effect on intestinal calcium absorption [27]. Close monitoring of serum calcium levels is essential to avoid hypercalcemia, a potential side effect of supplementation, particularly in patients with pre-existing hypercalcemia or at risk of developing it. This may necessitate adjusting the Vitamin D dose or using calcium-binding medications [27]. The evidence regarding the impact of Vitamin D supplementation on phosphate levels in CKD remains mixed: Studies by Locatelli et al. (2002) [20] and Molnar et al. (2013) [28] show contrasting findings, with some

suggesting potential benefits in lowering phosphate levels and others showing no significant effect.

Vitamin D's primary influence on phosphate metabolism is likely indirect, mediated through its effect on calcium and parathyroid hormone (PTH) levels. By promoting calcium absorption and suppressing PTH secretion, Vitamin D may indirectly contribute to lower phosphate levels [29]. More research is needed to explore the mechanisms by which Vitamin D supplementation might influence phosphate levels and its potential long-term impact on CKD-MBD management [29]. Some studies suggest that Vitamin D supplementation can contribute to PTH suppression in CKD patients [30]. Because Vitamin D promotes calcium absorption, reducing the need for PTH secretion by the parathyroid glands to maintain calcium homeostasis. Supplementation can help normalize PTH levels, potentially mitigating the detrimental effects of secondary hyperparathyroidism on bone health and cardiovascular function in CKD [30]. Studies like Henrich et al. (2011) [31] have shown that Vitamin D supplementation in conjunction with standard CKD-MBD treatment protocols can lead to a more significant reduction in PTH levels compared to placebo.

Impact on other aspects of CKD management

While the primary focus of Vitamin D supplementation in CKD is on improving bone health and mineral homeostasis in MBD, there's growing interest in its potential impact on other aspects of CKD management:

Vitamin D deficiency has been linked to muscle weakness and impaired physical function in various populations. Studies like Cessation of Dialysis Trialists' Collaborative Group (2010) [32] suggest that Vitamin D supplementation in dialysis patients may improve muscle strength and function. However, more research

is required to confirm these findings and elucidate the underlying mechanisms.

CKD patients are at high risk for cardiovascular complications. Vitamin D's potential anti-inflammatory and vascular protective effects are being explored [33]. Observational studies suggest an association between Vitamin D deficiency and cardiovascular events in CKD. However, RCTs haven't yet established a definitive cause-and-effect relationship regarding Vitamin D supplementation and improved cardiovascular outcomes in this population [34]. Further research is necessary to determine if Vitamin D supplementation can contribute to a comprehensive cardiovascular risk reduction strategy in CKD.

Vitamin D's role in modulating the immune system is well recognized. CKD patients have a higher susceptibility to infections. Studies are underway to explore whether Vitamin D supplementation can enhance immune function and reduce infection risk in CKD, but more research is needed to establish conclusive evidence [35].

Vitamin D supplementation regimens and considerations

Given the complexities discussed above, determining the optimal Vitamin D supplementation regimen for CKD patients requires careful consideration of several factors:

Measuring serum 25(OH) D levels is crucial to assess Vitamin D status and guide supplementation decisions. Most experts recommend targeting sufficient levels (>30 ng/mL) for optimal bone and overall health in CKD patients [34]. Vitamin D supplementation regimens for CKD patients typically involve higher doses compared to the general population due to impaired kidney activation and increased needs. However, individualized dosing based on baseline vitamin D levels, response to therapy, and potential risks of hypercalcemia is essential [34].

In some cases, activated vitamin D analogs like alfacalcidol (1-alpha-hydroxyvitamin D3) may be prescribed by nephrologists to address vitamin D deficiency and its effects on calcium and PTH levels in CKD patients with severely impaired kidney function [35]. Regular monitoring of serum calcium, phosphate, and PTH levels is necessary during Vitamin D supplementation to ensure safety and adjust the regimen as needed.

The Vitamin D supplementation is often incorporated into a comprehensive CKD-MBD treatment plan that may include calcium-regulating binders, phosphate binders, and medications to manage PTH levels.

Conclusion

Vitamin D deficiency is highly prevalent in CKD patients and contributes to MBD pathogenesis. While evidence suggests potential benefits of Vitamin D supplementation in improving bone mineral density, suppressing PTH levels, and potentially mitigating muscle weakness, the overall data on fracture risk reduction and impact on other aspects of CKD management remains inconclusive. Further research is needed to establish definitive recommendations for Vitamin D supplementation strategies in CKD, considering factors like optimal dosing, treatment duration, and potential interactions with other medications.

Future directions

Conduct larger, well-designed RCTs with standardized protocols and longer follow-up periods to definitively assess the impact of Vitamin D supplementation on various outcomes in CKD patients. Explore the potential benefits of Vitamin D for specific subgroups within the CKD population, such as patients at high risk for fractures or with limited sun exposure. Investigate the

combined effects of Vitamin D supplementation with other treatment modalities for a more comprehensive approach to CKD-MBD management. Elucidate the mechanisms by which Vitamin D supplementation might influence phosphate metabolism and its long-term impact on CKD.

By addressing these knowledge gaps, healthcare professionals can refine Vitamin D supplementation strategies and optimize patient care in CKD management.

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Ethics approval

No applicable.

Data availability

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Authors' contribution

Abdul Wahid and Abdul Ghaffar both significantly contributed to the conception, design, and writing of this review article. Ghulam Mustafa led the literature search, while Abdul Ghaffar contributed to the critical revision and editing of the manuscript. Abdul Wahid read and approved the final version of the manuscript.


Competing interests

The authors have diligently stated that they have no conflicts of interest to report.

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