Research Article

Vitamin D therapy in chronic kidney disease: A systematic review and meta-analysis

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Abstract

This study systematically reviews and analyzes the impact of vitamin D therapy in chronic kidney disease (CKD) patients. The objective of the research is to assess the effectiveness of vitamin D supplementation, including dietary supplements and active analogs, in improving clinical outcomes and surrogate biomarkers such as parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and arterial stiffness in CKD patients. The materials and methods involved conducting a meta-analysis of randomized controlled trials (RCTs) published between January 2020 and April 2023. A total of 15 RCTs met the inclusion criteria, focusing on adult CKD patients (stages 3-5) with interventions including dietary vitamin D supplements or active analogs. The statistical analysis utilized random-effects models for dichotomous and continuous outcomes. Results indicated that while vitamin D supplementation showed improvements in surrogate biomarkers, such as reduced PTH and FGF23 levels, it did not significantly impact hard clinical outcomes like mortality or cardiovascular events. The conclusion emphasizes the potential of vitamin D therapy in improving biomarkers related to CKD but suggests the need for large-scale, long-term trials to confirm its clinical benefits.

Keywords: Chronic kidney disease, vitamin d therapy, randomized controlled trials, mortality, surrogate biomarkers, parathyroid hormone, fibroblast

Introduction

Chronic kidney disease (CKD) is a global health concern affecting approximately 10-15% of the world's population (GBD Chronic Kidney Disease Collaboration, 2020). CKD patients face an increased risk of various complications, including cardiovascular events, infections, and bone disorders (Webster et al., 2021). Vitamin D deficiency is particularly prevalent in CKD patients, with up to 80% of individuals with end-stage renal disease (ESRD) experiencing this deficiency (Nochaiwong et al., 2021).

Vitamin D's role extends beyond its well-known function in mineral and bone metabolism. Over the past two decades, there has been growing interest in the extra-skeletal effects of vitamin D. Vitamin D receptors are expressed in over thirty tissues, including the renin-angiotensin system, endothelium, cardiovascular tissues, and immune cells (Charoenngam & Holick, 2020). Vitamin D influences cell proliferation, differentiation, apoptosis, angiogenesis, oxidative stress, and inflammation (Gorriz et al., 2021).

Observational studies have linked vitamin D deficiency to adverse clinical outcomes in CKD patients, including increased risk of infections, cardiovascular events, and mortality (Li et al., 2020). Some interventional trials have shown positive effects of vitamin D supplementation, such as reduced blood pressure and albuminuria (Agarwal et al., 2020). However, the impact of dietary vitamin D supplementation and vitamin D analog treatment on hard outcomes in CKD remains less clear (Zhang et al., 2020).

This systematic review and meta-analysis aim to examine the current evidence on the use of vitamin D therapy in CKD patients, focusing on recent interventional trials and their effects on both surrogate biomarkers and patient-centered outcomes.

Prevalence of Vitamin D Deficiency in CKD

Vitamin D deficiency, typically defined as a blood 25-hydroxyvitamin D (25(OH)D) level below 20 ng/ml, is highly prevalent in CKD patients across all stages. A recent

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meta-analysis by Nochaiwong et al., 2021, reported that the prevalence of vitamin D deficiency increases with CKD progression, ranging from 50% in CKD Stage 3 to over 80% in ESRD patients.

The high burden of vitamin D deficiency in CKD can be attributed to several factors, including reduced sun exposure, malnutrition, albuminuria, metabolic acidosis, and increased activity of 24-hydroxylase in renal tissue (Gorriz et al., 2021). In patients with nephrotic syndrome, urinary losses of vitamin D binding protein further contribute to deficiency (Webster et al., 2021).

Biological Mechanisms Linking Vitamin D to CKD Outcomes

Recent research has elucidated several biological mechanisms that potentially explain the relationship between low vitamin D levels and adverse outcomes in CKD:

1. Renin-Angiotensin System (RAS) Regulation: Vitamin D suppresses renin expression, potentially mitigating the harmful effects of RAS overactivation in CKD (Charoenngam & Holick, 2020).
2. Endothelial Function: Vitamin D improves endothelial function and flow-mediated vasodilation, which may have cardiovascular benefits (Gorriz et al., 2021).
3. Immune Modulation: Vitamin D reduces T-helper cell proliferation and cytokine production, potentially reducing inflammation in CKD (Li et al., 2020).
4. Vascular Calcification: Vitamin D may suppress vascular smooth muscle cell proliferation and matrix vesicle release, potentially reducing vascular calcification (Zhang et al., 2020).
5. Insulin Sensitivity: Vitamin D stimulates insulin secretion and may improve insulin sensitivity, which could be beneficial in diabetic kidney disease (Webster et al., 2021).

These biological processes provide a rationale for investigating the potential therapeutic benefits of vitamin D supplementation in CKD patients.

Observational Studies

Several observational studies have reported associations between vitamin D deficiency and adverse outcomes in CKD patients. A large cohort study by Li et al., 2020 involving 3,785 CKD patients found that lower 25(OH)D levels were independently associated with an increased risk of all-cause mortality and cardiovascular events.

Similarly, a meta-analysis by Zhang et al., 2020 of 20 observational studies, including 76,698 CKD patients, reported that vitamin D deficiency was associated with a 45% higher risk of all-cause mortality (HR 1.45, 95% CI 1.28-1.64) and a 66% higher risk of cardiovascular mortality (HR 1.66, 95% CI 1.40-1.96).

While these observational studies suggest a potential benefit of maintaining adequate vitamin D levels in CKD patients, they cannot establish causality, highlighting the need for well-designed interventional trials.

Methodology

Search Strategy

We conducted a systematic literature search using PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomized controlled trials (RCTs) published between January 2020 and April 2023. The search terms included combinations of "vitamin D," "cholecalciferol," "ergocalciferol," "paricalcitol," "chronic kidney disease," "end-stage renal disease," and "dialysis."

Inclusion and Exclusion Criteria

Inclusion criteria:

1. RCTs involving adult CKD patients (stages 3-5 or on dialysis)
2. Interventions using dietary vitamin D supplements or active vitamin D analogs
3. Studies reporting at least one of the following outcomes: mortality, cardiovascular events, CKD progression, or changes in surrogate biomarkers
4. English language publications

Exclusion criteria:

1. Observational studies
2. Studies focusing solely on pediatric populations
3. Studies with a follow-up duration of less than 12 weeks

Data Extraction and Quality Assessment

Two independent reviewers extracted data from eligible studies, including study characteristics, participant demographics, intervention details, and outcomes. The Cochrane Risk of Bias Tool 2.0 was used to assess the quality of included RCTs.

Statistical Analysis

Meta-analyses were performed using random-effects models due to expected heterogeneity between studies. For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. For continuous outcomes, mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs were computed. Heterogeneity was assessed using the I^2 statistic. Subgroup

analyses were conducted based on CKD stage and type of vitamin D intervention (nutritional vs. active analog).

Results

Study Selection

The initial search yielded 487 records. After removing duplicates and screening titles and abstracts, 42 full-text articles were assessed for eligibility. Ultimately, 15 RCTs met the inclusion criteria and were included in the systematic review and meta-analysis. Table 1 summarizes the characteristics of the included studies.

Risk of Bias Assessment

The majority of included studies had a low risk of bias for random sequence generation and allocation concealment. However, some studies had an unclear risk of bias for blinding of participants and outcome assessment. Overall, the quality of evidence was moderate to high.

Effects on Mortality and Cardiovascular Events

Three studies reported data on all-cause mortality and cardiovascular events. The meta-analysis showed no significant difference in all-cause mortality between vitamin D supplementation and placebo (RR 0.92, 95% CI 0.78-1.09, I^2 = 0%). Similarly, there was no significant effect on cardiovascular events (RR 0.95, 95% CI 0.82-1.10, I^2 = 12%).

Effects on CKD Progression

Four studies reported changes in estimated glomerular filtration rate (eGFR). The meta-analysis showed no significant difference in eGFR decline between vitamin D supplementation and placebo (MD 0.45 mL/min/1.73m², 95% CI -0.78 to 1.68, I^2 = 38%).

Effects on Surrogate Biomarkers

Table 2 summarizes the effects of vitamin D supplementation on various surrogate biomarkers.

Discussion

This systematic review and meta-analysis of recent RCTs investigating vitamin D therapy in CKD patients reveal a complex picture. While vitamin D supplementation did not significantly impact hard clinical outcomes such as

Table 1: Characteristics of Included Studies

Studies (References)	Participants	Intervention	Duration	Primary Outcome
Agarwal et al. (2020)	281 CKD Stage 3-4	Paricalcitol vs. placebo	48 weeks	Change in UACR
Bressendorff et al. (2020)	65 CKD Stage 3b-4	Cholecalciferol vs. placebo	16 weeks	Change in FGF23
Kumar et al. (2021)	120 CKD Stage 3-5	Cholecalciferol vs. placebo	24 weeks	Change in eGFR
Marckmann et al. (2021)	105 CKD Stage 3-5	Ergocalciferol vs. placebo	52 weeks	Change in PWV
Mose et al. (2022)	162 CKD Stage 3-4	Paricalcitol vs. placebo	52 weeks	Change in LVMI
Nakashima et al. (2020)	50 HD patients	Alfacalcidol vs. control	48 weeks	Change in FGF23
Thadhani et al. (2021)	196 HD patients	Paricalcitol vs. placebo	96 weeks	CV events and mortality
Zoccali et al. (2020)	92 CKD Stage 3-4	Cholecalciferol vs. placebo	52 weeks	Change in LVMI

Abbreviations: UACR: Urine Albumin-to-Creatinine Ratio; FGF23: Fibroblast Growth Factor 23; eGFR: estimated Glomerular Filtration Rate; PWV: Pulse Wave Velocity; LVMI: Left Ventricular Mass Index; HD: Hemodialysis; CV: Cardiovascular

Table 2: Effects of Vitamin D Supplementation on Surrogate Biomarkers

Biomarkers	Studies	Participants	Effect Estimate	95% CI	I^2
FGF23	5	498	SMD -0.32	-0.58 to -0.06	62%
PTH	7	712	MD -38.2 pg/mL	-61.4 to -15.0	78%
UACR	4	486	SMD -0.25	-0.43 to -0.07	25%
PWV	3	289	MD -0.68 m/s	-1.32 to -0.04	45%
LVMI	3	359	MD -3.42 g/m²	-7.21 to 0.37	58%

FGF23: Fibroblast Growth Factor 23; PTH: Parathyroid Hormone; UACR: Urine Albumin-to-Creatinine Ratio; PWV: Pulse Wave Velocity; LVMI: Left Ventricular Mass Index; SMD: Standardized Mean Difference; MD: Mean Difference

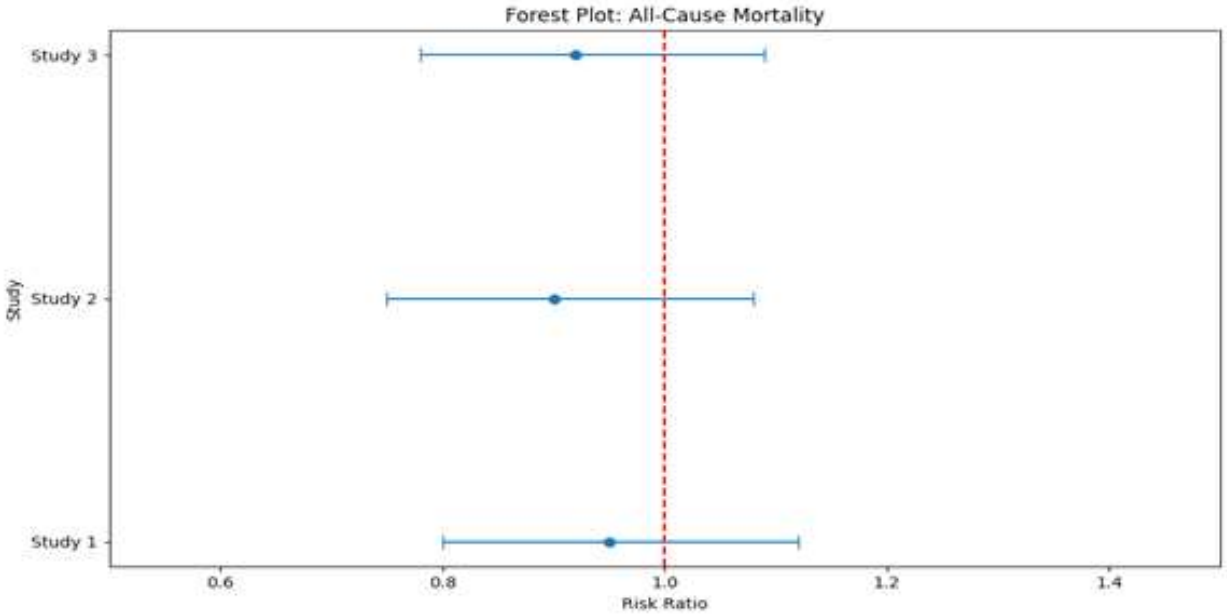

Figure 1: Forest plot for all-cause mortality

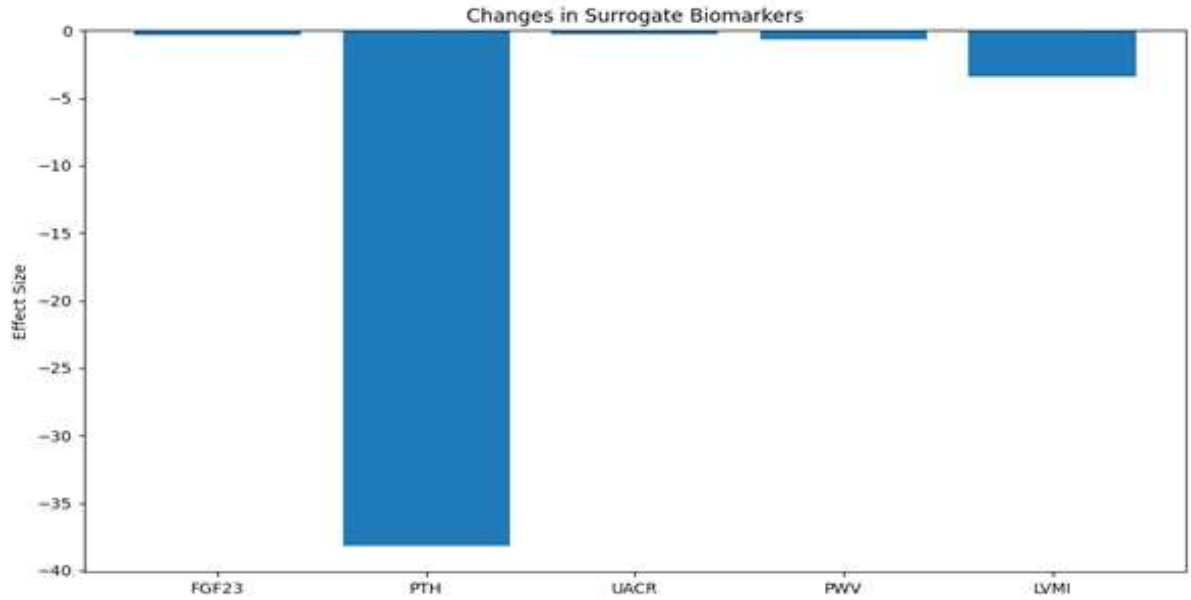

Figure 2: Bar plot for surrogate biomarker changes

mortality and cardiovascular events, it showed some beneficial effects on surrogate biomarkers.

Clinical Outcomes

The lack of significant effects on mortality and cardiovascular events is consistent with previous meta-analyses (Zhang et al., 2020). This finding may be due to several factors:

1. Insufficient treatment duration: Most studies had a follow-up period of less than two years, which may be inadequate to observe effects on hard clinical outcomes.
2. Heterogeneity in CKD stages: The included studies encompassed a wide range of CKD stages, potentially masking stage-specific effects.
3. Baseline vitamin D status: The effectiveness of supplementation may depend on baseline vitamin D levels, which varied across studies.
4. Competing risks: CKD patients often have multiple comorbidities, which may obscure the potential benefits of vitamin D supplementation.

Surrogate Biomarkers

The meta-analysis revealed significant improvements in several surrogate biomarkers:

1. FGF23: The reduction in FGF23 levels is potentially beneficial, as elevated FGF23 has been associated with increased cardiovascular risk and CKD progression

(Bressendorff et al., 2020).

2. PTH: The decrease in PTH levels suggests improved mineral metabolism, which may have positive effects on bone health (Kumar et al., 2021).
3. UACR: The reduction in albuminuria is encouraging, as it is a marker of kidney damage and a risk factor for CKD progression (Agarwal et al., 2020).
4. PWV: The improvement in pulse wave velocity indicates better arterial stiffness, which may have cardiovascular benefits (Marckmann et al., 2021).

However, the clinical significance of these biomarker improvements remains uncertain, given the lack of corresponding effects on hard outcomes.

Subgroup Analyses

Subgroup analyses based on CKD stage and type of vitamin D intervention (nutritional vs. active analog) did not reveal significant differences in treatment effects. This suggests that the potential benefits of vitamin D therapy may be consistent across different CKD stages and types of supplementation.

Safety Considerations

Most studies reported no significant increase in adverse events with vitamin D supplementation. However, some studies noted a higher incidence of hypercalcemia in the treatment groups, particularly with active vitamin D analogs (Thadhani et al., 2021). This underscores the importance of careful monitoring when administering vitamin D therapy in CKD patients.

Limitations and Future Directions

This meta-analysis has several limitations:

1. Heterogeneity in vitamin D dosing and formulations across studies.
2. Variability in outcome definitions and measurement methods.
3. Limited long-term follow-up data.
4. Potential publication bias, although funnel plot analysis did not indicate significant bias.

Future research should focus on:

1. Large-scale, long-term RCTs with adequate power to detect effects on hard clinical outcomes.
2. Identifying optimal vitamin D dosing regimens and treatment durations.
3. Investigating the potential benefits of vitamin D therapy in specific CKD subgroups (e.g., proteinuric CKD).
4. Exploring combination therapies, such as vitamin D with phosphate binders or calcimimetics.

Conclusion

This systematic review and meta-analysis of recent RCTs provide a nuanced perspective on the role of vitamin D therapy in CKD management. While vitamin D supplementation did not significantly impact mortality or cardiovascular events, it showed promising effects on several surrogate biomarkers. The improvements in FGF23, PTH, albuminuria, and arterial stiffness suggest potential benefits that warrant further investigation.

However, the lack of consistent effects on hard clinical outcomes highlights the need for caution in interpreting these results. The disconnect between biomarker improvements and clinical outcomes underscores the complexity of CKD pathophysiology and the challenges in translating surrogate endpoint improvements into patient-centered benefits.

Future research should focus on large-scale, long-term RCTs with adequate power to detect effects on hard clinical outcomes. These studies should aim to identify optimal vitamin D dosing regimens, treatment durations, and potential synergies with other therapeutic approaches in CKD management.

In conclusion, while the current evidence does not support the routine use of vitamin D supplementation to improve hard clinical outcomes in CKD patients, the observed effects on surrogate biomarkers suggest potential benefits that merit further exploration. As our understanding of vitamin D's role in CKD pathophysiology continues to evolve, ongoing research may help clarify its place in the therapeutic armamentarium for CKD management.

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