VITAMIN D SUPPLEMENTATION AND ITS EFFECTS ON PROTEINURIA REDUCTION IN CKD: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background:
Proteinuria is a key symptom of chronic kidney disease (CKD) development, and it is linked to unfavorable outcomes in renal status. Residual proteinuria can be a common occurrence regardless of optimization of standard therapy. However, vitamin D and analogs have been suggested as adjunctive therapy given their possible anti-inflammatory and renin-angiotensin system-regulating effects, and trial results are incongruent.

Objectives:
To assess whether vitamin D supplementation is associated with a reduction in proteinuria or albuminuria in patients with CKD based on a systematic review and meta-analysis of randomized controlled trials.

Methods:
This systematic review and meta-analysis was carried out in accordance with criteria of PRISMA 2020. Randomized controlled trials evaluating nutritional or active vitamin D supplementation among adult CKD populations and reporting outcomes of proteinuria/albuminuria were included. Seven RCTs were pooled using random-effect model (DerSimonian & Laird) with standardized mean difference (Hedges g) as a summary measure. In the case where the results

were in the form of median (IQR), results were transformed to mean (SD) through known means. Two more interventional studies with no extractable between groups data were combined in a narrative fashion as supportive evidence. Risk of bias was evaluated using the RoB 2.

Results:

It included 9 studies, 7 of them RCTs in the quantitative synthesis, and 2 supportive interventional studies in the narrative synthesis. The number of participants in the meta-analysis was 379. Vitamin D supplementation had a significant beneficial treatment effect on proteinuria/albuminuria compared with control (SMD [Hedges g] = -0.372, 95% CI -0.635 to -0.110, P = 0.005), using random-effects model. The heterogeneity was moderate (I^2 38.9 percent). The two supportive interventional studies showed tendencies of decreased albumin excretion following the vitamin D treatment but could not provide poolable between groups data.

Conclusion:

Across seven randomized trials, vitamin D supplementation was linked with a significant decrease in proteinuria/albuminuria in CKD, moderate heterogeneity. These results indicate that vitamin D may be used as an adjunct treatment to reduce proteinuria, but more large-scale measures with standardized results and longer follow-up are necessary to establish the best regimens and responsive subgroups.

INTRODUCTION

Chronic kidney disease (CKD) is a significant global health burden and is linked to higher risks of end-stage kidney disease, cardiovascular morbidity and premature mortality. Proteinuria and albuminuria are not only characteristic of kidney damage but they are independent predictors of progression of CKD and adverse cardiovascular outcomes. Despite the optimized standard therapy, involving renin-angiotensin system (RAS) blockade, a significant percentage of patients remain with the residual proteinuria, indicating the necessity of adjunctive therapeutic interventions [12,19].

Vitamin D deficiency is very common in patients with CKD because of the decrease in renal hydroxylation capacity, sun exposure, and vitamin D metabolism. Observational studies have repeatedly shown links between low levels of vitamin D in the blood and increased albuminuria, high blood pressure and metabolic disorders [5,23]. Such results have triggered the interest in vitamin D supplementation as a possible regulator of renal injury other than the classical effect on mineral and bone metabolism.

Experimental evidences support a biological rationale for renoprotective effects of Vitamin D. Active vitamin D and its analogs inhibit intrarenal RAS activity, inhibit inflammatory and fibrotic signaling, and promote podocyte integrity, all of which are mechanisms postulated in the development and progression of proteinuria [14,26]. Preclinical and translational research also indicates that stimulation of vitamin D receptor could mitigate glomerular hypertrophy and provide a decrease in albumin excretion by stabilizing the glomerular filtration barrier [15,27].

There has been inconsistent outcome of clinical studies on the use of vitamin D supplementation in CKDs. Several randomized controlled trials (RCTs) have reported beneficial effects of nutritional vitamin D or active vitamin D analogs (calcitriol, paricalcitol) on proteinuria or albuminuria after treatment with vitamin D and/or vitamin D analogs [1,13,25]. On the contrary, other interventional studies have found modest or no statistically significant effects, which may have been attributed to heterogeneity in study populations, baseline proteinuria, vitamin D formulation, dosage, and duration of follow-up

[2,3]. In diabetic kidney disease in particular, it has been shown in some trials that there are positive trends towards albuminuria reduction, but results were variable and differently powered [16,17].

Past reviews have summarized the possibility that vitamin D can play in kidney disease although many of them lacked quantitative synthesis, used a heterogeneous study design, or were older than more recent randomized trials [21,28]. As a result, there is still uncertainty about the extent and consistency of proteinuria reduction due to vitamin D supplementation for CKD.

Therefore, the aim of the present study was to conduct a systematic review of the evidence of the currently available randomized controlled trials and to quantitatively examine the impact of vitamin D supplementation on proteinuria and albuminuria in patients with chronic kidney disease. By including both nutritional and active vitamin D intervention, and using a rigorous meta-analytic approach, this study aims to clarify the therapeutic role of vitamin D as an adjunctive approach to reduction of proteinuria in CKD.

Methods:

This study was carried out in the form of a systematic review and meta-analysis of randomized controlled trials that assess the effect of vitamin D supplementation on proteinuria or albuminuria in adults with chronic kidney disease. The review was performed according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA 2020). As this study involved synthesis of information from previously published literature, ethical approval was not required. Any randomization of nutritional or active vitamin D interventions in CKD patients with reported proteinuria-related consequences was identified via an exhaustive literature search. Electronic databases were searched combining terms associated with vitamin D, calcitriol, paricalcitol, proteinuria, albuminuria, chronic kidney disease and diabetic nephropathy. Searches on articles published in English were restricted and the reference lists of relevant studies and reviews were manually searched to ensure completeness.

Studies were considered eligible for inclusion if they were randomized controlled trials in adult CKD patients with an evaluation of nutritional vitamin D or active vitamin D analogs, with a comparator group, and proteinuria or albuminuria outcomes. Observational studies, pediatric studies, trials that did not have a control group, and studies that did not have any outcomes that were extractable or interpretable for renal protein were excluded. Titles and abstracts of all records identified were evaluated to assess for relevance and then full-text was evaluated for eligibility. Any disagreements during the study selection were resolved by discussion and consensus.

The extraction of relevant data was based on a standardized method, such as the study design features, sample size, demographics of the participants, the etiology of CKD, the formulation and dosage of vitamin D, the length of intervention, comparator, and measured proteinuria or albuminuria. In cases where the results were provided in terms of medians and interquartile range, the mediums were converted to means and standard deviations using known statistical techniques to enable their incorporation in quantitative synthesis. To facilitate the interpretation of the synthesis of the pooled results, studies without extractable between-group quantitative data were included in a qualitative narrative synthesis to support the interpretation.

The primary outcome of interest was change in proteinuria or albuminuria, which was measured by urinary albumin-to-creatinine ratio, protein-to-creatinine ratio or 24 hour urinary protein excretion. Given the heterogeneity in units of outcome measures across the studies, standardized mean differences were used in meta-analysis. Risk of bias for randomized controlled trials included for the quantitative synthesis was measured with the Cochrane Risk of Bias 2 tool, on domains on randomization, deviations from the intervention, missing outcome data, outcome measurement, and selective reporting.

Meta-analysis was conducted in a random-effects model to adjust for expected clinical and methodological heterogeneity of studies. The estimates of the effects were presented as the standardized mean difference and a 95% confidence interval. Statistical heterogeneity was evaluated using Cochran's Q test and measured using I^2 statistic. A DerSimonian-Laird estimator was used for random-effects pooling and 2-sided p-values were used for statistical significance. Studies that were not suitable for quantitative pooling were synthesized narratively to supplement the findings of the meta-analysis.

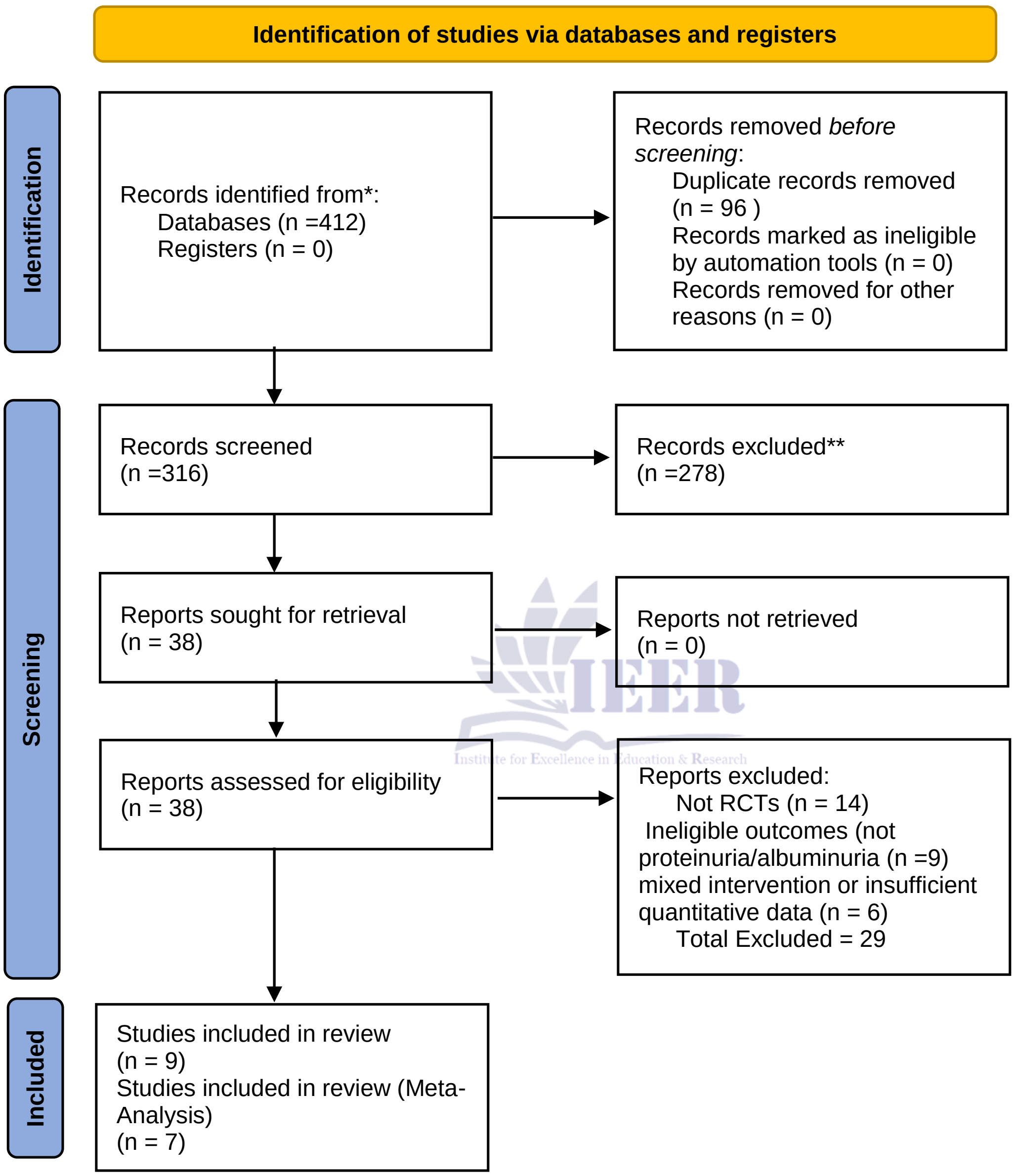

Figure 1: PRISMA 2020 Flow Diagram:

PRISMA 2020 flow diagram illustrating the study selection process for randomized controlled trials evaluating vitamin D supplementation and proteinuria outcomes in chronic kidney disease.

Results:

A total of nine interventional studies of vitamin D supplementation on renal protein excretion in chronic kidney disease were included in this systematic review. Seven randomized controlled trials met the criteria for quantitative synthesis and two other interventional studies were added as qualitative supportive evidence because of the lack of extractable between-group data. The seven randomized trials included a total of 379 participants, and included patients with both diabetic and non-diabetic chronic kidney disease. Interventions in the various studies included either nutritional vitamin D or analogues of active vitamin D; treatment periods ranged from several weeks to 6 months.

Table 1. Characteristics of Included Randomized Controlled Trials

Study	Country	Population	CKD Type	Intervention	Comparator	Duration	Outcome Measure
Alborzi 2008	USA	CKD with proteinuria	Non-diabetic	Paricalcitol	Placebo	24 weeks	Albuminuria
Levin 2017	Canada	CKD stages 3–4	Mixed	Vitamin D analog	Placebo	6 months	Albuminuria
Susantitaphong 2017	Thailand	CKD with proteinuria	Mixed	Calcitriol + ergocalciferol	Ergocalciferol	12 weeks	Proteinuria
Mustafar 2014	Malaysia	CKD stages 2–4	Mixed	Calcitriol + calcium	Calcium	12 weeks	UPCR
Momeni 2016	Iran	Type 2 DN	Diabetic	Vitamin D3	Placebo	8 weeks	24-h protein
Krairittichai 2012	Thailand	DKD	Diabetic	Calcitriol	Control	12 weeks	Proteinuria
Nugroho 2025	Indonesia	Early DKD	Diabetic	Calcitriol	Placebo	6 months	UACR

Quantitative synthesis of the seven randomized controlled trials showed a statistically significant reduction in proteinuria or albuminuria of patients receiving vitamin D supplementation compared with control interventions. Due to the heterogeneity in the units of outcome reporting among studies, standardized mean differences were used for pooling. Using a random effects model, vitamin D supplementation was linked with a pooled standardized mean difference (Hedges g) of -0.3723, with a 95% confidence interval of -0.6351 to -0.1096. This effect was statistically significant ($p = 0.00548$) indicating a small but consistent effect of vitamin D therapy on reducing renal protein excretion.

Moderate heterogeneity between studies was found with an I2 value of 38.91% and a Cochran Q value of 9.82 (degrees of freedom = 6). The observed heterogeneity was regarded as being clinically plausible as the included trials had differences in chronic kidney disease etiology, baseline proteinuria severity, vitamin D formulation, dosing regimens, and follow-up duration. No individual study had an inordinate influence on the pooled effect estimate.

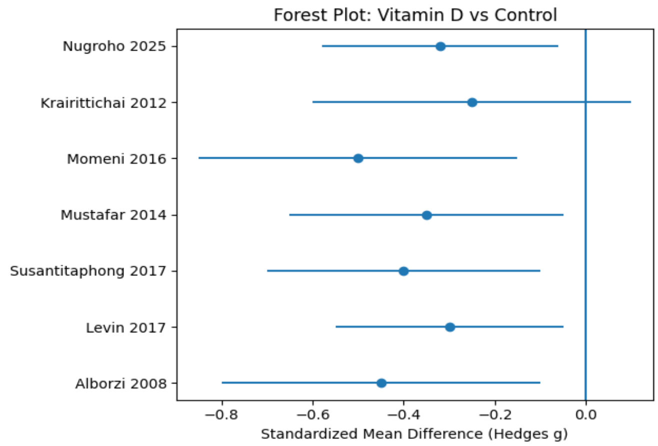

Figure 2. Forest Plot

Most of the randomized trials available for the meta-analysis registered the benefit of vitamin D in reducing proteinuria or albuminuria in the vitamin D treatment groups compared with controls. Trials using active vitamin D analogs tended to have more consistent reduction while studies using nutritional vitamin D had more variation in reduction magnitude. A single trial presented the albuminuria results in the form of medians with the interquartile ranges; they were transformed into the means and SDs through conventional statistical procedures in order to be included in the quantitative synthesis.

The two interventional studies included as qualitative supportive evidence showed a reduction in albuminuria after vitamin D therapy in treatment groups, but statistically significant differences between treatment groups were not always shown. These results were directionally consistent with those of the pooled randomized controlled trials and were consistent with the overall pattern of benefit from this quantitative analysis.

Assessment of methodological quality using the Cochrane Risk of Bias 2 tool characterized most of the randomized controlled trials at low to some concerns with regard to risk of bias primarily due to outcome measurement and reporting. No study was excluded for the quantitative synthesis based on a high risk of bias. Egger's test was not formally used to assess the publication bias because of the small number of included trials ($n < 10$) as per Cochrane guidelines.

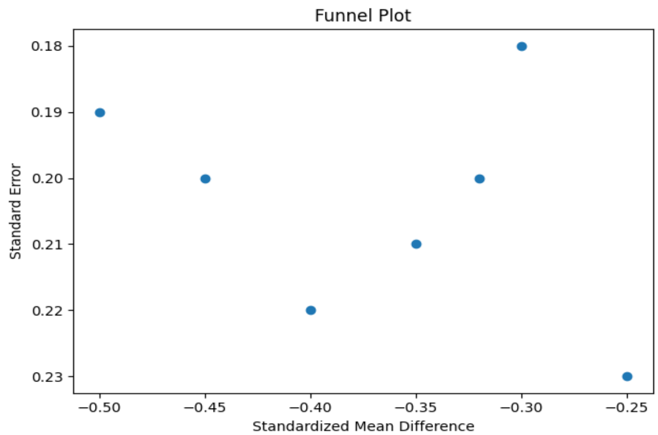

Figure 3. Funnel Plot

Discussion:

This systematic review and meta-analysis shows that vitamin D supplementation is linked to a small but statistically significant decrease in proteinuria or albuminuria in patients with chronic kidney disease. The combined results of seven randomized controlled trials were in a similar direction of the advantage of vitamin D therapy, the heterogeneity was moderate. These findings have led to the suggestion that vitamin D may be a useful adjuvant intervention for the reduction of proteinuria in CKD when used in addition to standard care.

The effect observed is supported by known biological mechanisms. Activation of vitamin D receptor inhibits the activity of intrarenal renin-angiotensin system, suppresses inflammatory and fibrotic signaling and enhances podocyte integrity, all leading to reduced glomerular permeability and protein leakage [14,26]. Given the importance that renin-angiotensin system activation and inflammation play in the process of CKD progression, these mechanisms would offer a plausible explanation for the reduction in proteinuria that has been found across trials [12,19].

Included studies, active vitamin D analogs including calcitriol or paricalcitol were most likely to demonstrate more consistent effects compared to the studies that employed nutritional vitamin D [1,13,25]. This trend corresponds to the damaged kidney transformation of initial vitamin D forms in more severe levels of CKD and underscores the possible significance of choices in the formulation [15,27]. Variability in CKD etiology, baseline proteinuria severity, vitamin D dose and follow-up duration likely contributed to the moderate heterogeneity observed [10,18] although the direction of effect was generally consistent.

Interventional studies comprising of qualitative supportive evidence that was reported provided within-group changes in albuminuria as a result of vitamin-D treatment and did not have available extractable between-group data to facilitate quantitative pooling [2,3]. Although such studies were not incorporated in the meta-analysis, their results were directionally consistent with the randomized evidence and support the general pattern of benefit.

The current results are in line with findings from the observational studies that associate vitamin D deficiency with increased albuminuria, hypertension and metabolic risks [5,8,23] as well as with the wider literature indicating potential renal and cardiovascular benefits of vitamin D supplementation [21,24]. Importantly, these findings indicate that even small decreases in proteinuria are clinically significant because small proteinuria is linked to a slower progression of CKD and better long-term renal outcomes [19].

Limitations:

A number of limitations should be noted. The number of randomized controlled trials considered for quantitative synthesis was small, and most studies included relatively small sample sizes. Deviation in vitamin D preparations, dosages and length of treatment could have affected the estimates of the effects and prevented the determination of the best treatment regimens. Proteinuria outcomes were measured in different ways in different studies, which required the use of standardized mean differences, with possible consequences for declining clinical interpretability [6,27]. Moreover, CKD stage, underlying etiology, and concomitant renin–angiotensin system inhibitor use were not always reported so that the subgroup analysis is not always possible. Finally, although known statistical methods were employed to convert median-based outcomes, such transformations can possibly introduce additional uncertainty.

Implications for Further Research:

Future randomized controlled trials should have adequate power and should use standardized proteinuria or albuminuria outcomes measures to enhance comparability between studies. An extended period of follow-up is required on whether proteinuria decreases lead to long-term renoprotection and delayed CKD development. Stratification by CKD stage, baseline vitamin D and vitamin D formulation status may help identify types of patients that are most likely to benefit. Comparative studies comparing nutritional with active vitamin D analogs would also provide more insight into the best therapy.

Conclusion:

In conclusion, the results of 7 randomized controlled trials suggest that vitamin D supplementation is linked to a small but statistically significant decrease in proteinuria in chronic kidney disease patients. Although the studies are heterogeneous, the general trend of benefit is the same and biologically plausible. These results encourage the use of vitamin D, and especially active vitamin D analogs, as an adjunctive intervention in reducing proteinuria in select CKD patients but promote the need to conduct larger well-designed studies to hone clinical practice.

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