Review

Effect of Vitamin D on Urinary Albumin Excretion in Diabetic Nephropathy Patients: A Meta-analysis of Randomized Controlled Trials

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It remains controversial, whether vitamin D reduces urinary albumin excretion in patients with diabetic nephropathy (DN). This meta-analysis was designed to evaluate the therapeutic effect of vitamin D, on urinary albumin excretion, in DN patients.

Electronic databases, including PubMed, Embase, Web of Science, and Cochrane library were searched for randomized controlled trials (RCTs), regarding the effect of vitamin D on urinary albumin excretion in DN patients. The study selection and data extraction were conducted by two reviewers independently, and statistical analysis was performed using RevMan software, version 5.2.

A total of nine RCTs including 1547 subjects were qualified. There were 815 participants in the study group and 732 in the control group. The fixed-effect model was used to analyze urinary albumin creatinine ratio (UACR) and urinary albumin excretion ratio (UAER), and the pooled standard mean difference (SMD) was -0.24 (95% CI: -0.39 to -0.09), $P = .002$, and -0.57 (95% CI: -0.71 to -0.43), $P < .00001$; respectively. These findings indicated that vitamin D-treated patients had a statistically significant reduction in UACR and UAER. High-quality RCTs are still required.

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INTRODUCTION

Diabetic nephropathy (DN) is one of the most important complications of diabetes mellitus and is also the leading cause of chronic kidney disease (CKD). Patients with DN have progressive kidney dysfunction that is mostly accompanied by proteinuria. Therefore, reducing urinary albumin excretion in DN patients, can effectively protect kidney function and delay the progression of DN.

Vitamin D, particularly its active metabolite, 1α,25-dihydroxy vitamin D3, is an important hormone, the primary role of which is to regulate the metabolism of calcium and phosphorus metabolism. Epidemiological studies indicate that DN patients are more likely to develop vitamin D deficiency than the general population.[1] Vitamin D deficiency is quite prevalent and may play a role in the development of DN.[2] As a result, vitamin D supplementation for DN patients, has become a subject of interest. In recent years, a growing number of studies have revealed that vitamin D plays an important role in kidney protection[3,4]. Numerous randomized controlled trials (RCTs) have been conducted, on the impact of vitamin D supplementation on proteinuria in DN patients. In addition, a prior meta-analysis[5] demonstrated that vitamin D supplementation may have a favorable impact on inflammatory indices, as well as 24-

hour urine protein, in DN patients. However, it remains a matter of debate, whether vitamin D reduces urinary albumin excretion. Therefore, the purpose of this meta-analysis was to determine, the effect of vitamin D on reducing urinary albumin excretion in DN patients.

MATERIALS AND METHODS

Inclusion Criteria

Studies that met all of the following pre-specified eligibility criteria, were included in this meta-analysis: 1) RCTs on treating patients with DN; 2) studies that compared vitamin D (any dose, type) with placebo or blank control; 3) studies on the outcome of urinary albumin creatinine ratio (UACR) or urinary albumin excretion ratio (UAER); 4) studies with a minimal follow-up of 12 weeks.

Study Search and Selection

We searched the following databases: PubMed, Embase, Web of Science, and Cochrane library, from inception to 2022. The clinical trial register center (http://www.clinialtrials.gov) was also looked for additional trials. Vitamin D, cholecalciferol, paricalciferol, calcitriol, urinary albumin, albuminuria, diabetic nephropathy, diabetic kidney disease and randomized controlled trials, were utilized as search terms. According to the inclusion criteria, two reviewers independently screened the titles and abstracts. In cases where an article's eligibility was in doubt, the complete text was carefully reviewed. Authors were contacted to retrieve full-text articles, when not available otherwise. Reference lists from identified articles were also searched.

Data Extraction

Two reviewers independently extracted relevant data from all selected trials, regarding participant characteristics, medications, medication doses, follow-up, and treatment-related adverse events. Any further information required by writing correspondence, and any obtained relevant information, were included in the review. Conflicts were settled after consulting with an arbitrator.

Study Quality Assessment

The study quality was assessed by using the Cochrane Collaboration Tool, considering the following categories: 1) random sequence generation (selection bias); 2) Allocation concealment (selection bias); 3) blinding (performance and detection bias); 4) incomplete outcome data (attrition bias); 5) selective reporting (reporting bias); and 6) other bias.[6,7] Two reviewers determined these items independently, and any disagreements were resolved by consensus.

Statistical Analysis

RevMan software, version 5.2 was used to analyze the data. The outcomes were the changes in UACR and UAER from the baseline. The meta-analysis with the fixed model was performed by standard mean difference (SMD) for the outcome of continuous variables. All the results were estimated from each article, using a 95% confidence interval (CI). The chi-square test and I^2 statistics were used to assess heterogeneity between the studies. If P was more than .1 and I^2 was less than 50%, homogeneity was considered to exist, and a fixed-effect model was used for pooled analysis. Otherwise, a random-effect model was adopted, and the sensitivity analysis or subgroup analysis was undertaken to identify the source of heterogeneity and confirm the stability of the results. The Egger test was applied to examine publication bias, using funnel plots. $P < .05$ was considered statistically significant.

RESULTS

Trial Flow and Study Characteristics

The initial search strategy found 1535 citations and 91 were selected for full-text review, out of which, 9 articles met the inclusion criteria.[8-16] The flow diagram of the study selection is shown in Figure 1 and the main characteristics of the nine trials are summarized in Table.

Study Quality

The methodological quality of the included studies was shown in Figure 2. Based on the formal parameters, mentioned in the Cochrane Handbook, the quality of the majority of the studies was acceptable and only one study revealed a high risk of bias.[13] Some studies lacked sufficient information to judge reporting bias, attrition bias and other biases.[8-11,14]

Publication Bias and Sensitivity Analysis

Publication bias might have some effect on the results because the funnel plots of the included

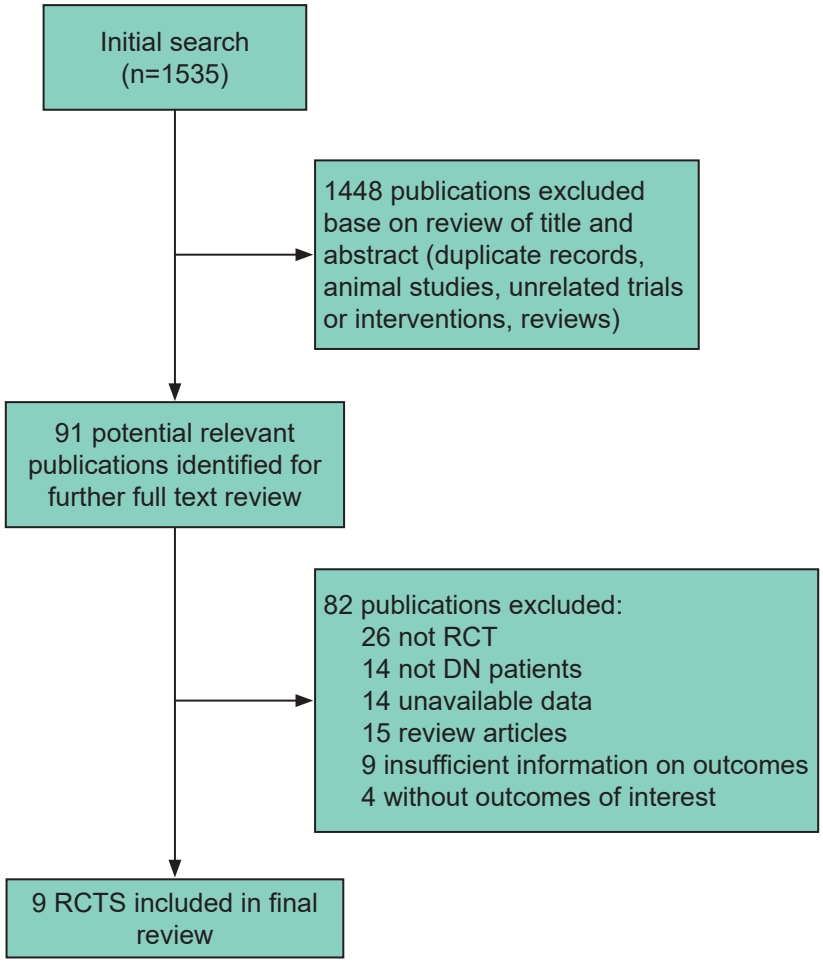

Figure 1. Flow Diagram of Study Selection (Vitamin D for DN Patients)

Characteristics of the Studies Included in the Meta-analysis

Author (Reference)	Year	Country	Population	Number (T/C)	Drug		Route	Follow-Up
					Treatment Group	Control Group		
He[8]	2017	China	T1DM + T2DM	30/30	Calcitriol 0.25 ug/d	Placebo	oral	12 w
Huang[9]	2012	China	T2DM	22/24	Cholecalciferol 800 IU/d	Placebo	oral	6 m
Momeni[10]	2017	Iran	T2DM	29/28	Vitamin D pearl 50000 IU/week	Placebo	oral	12 w
Tiryaki[11]	2016	Turkey	T2DM	48/50	Calcitriol 0.25 ug/d	Placebo	oral	24 w
Sakineh[12]	2011	Iran	T2DM	50/50	Calcitriol 500IU + 170 mg Ca bid	170 mg Ca bid	oral	12 w
Krairittichai[13]	2012	Thailand	T2DM	46/45	Calcitriol 0.5 mg bid	Placebo	oral	16 w
Ahmadi[14]	2013	Iran	T2DM	30/30	Calcitriol 50000 IU/W	Placebo	oral	2 m
De Zeeuw[15]	2010	Europe America	T2DM T2DM	95/93	High-dose group:2 ug/d Low-dose group:1 ug/d	Placebo	oral	24 w
Ian H de Boer[16]	2019	America	T2DM	370/289	Cholecalciferol 2000 IU/d	Placebo	oral	5 y

Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; T, treatment group; C, control group; bid, two times per day; below, two times per week

studies appeared to be asymmetrical. Since positive results are more likely to be published, it may cause a possible bias towards positive results. This is a major potential limitation of meta-analysis. Besides, we performed a sensitivity analysis to test the robustness of the results. The pooled estimates were recalculated by removing one study at a time, and the summary estimate effect remained unchanged. Sensitivity analysis suggested that the results had good stability.

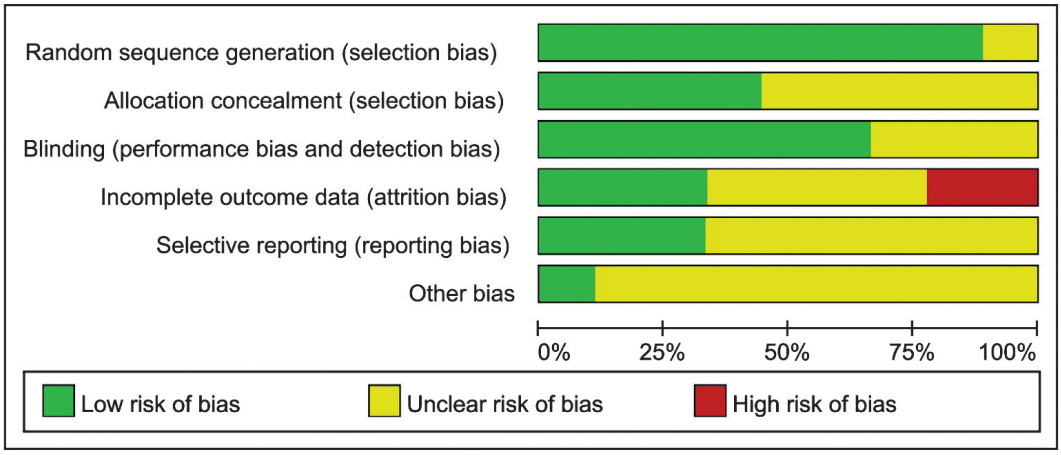

Figure 2. Methodological Quality of Included Studies

Outcome Measures

UACR. Five studies including 673 participants, 338 in the vitamin D treated group and 335 in the control group, were analyzed. All of the five studies had homogeneity (heterozygosity test, $Chi^2 = 5.58$, $P = .35$, $I^2 = 10\%$). A fixed-effect model was used to merge SMD values. The pooled data was -0.24 (95%CI: -0.39 to -0.09, Z = 3, $P = 0.002$; Figure 3), which indicated that there was a statistically significant reduction in UACR among vitamin D-treated patients.

UAER. Four studies that included 874 participants were analyzed. Four hundred and seventy- seven patients participated in the vitamin D-treated group, and 397 in the control group. All four studies had homogeneity (heterozygosity test, Chi2 = 4.51, $P = .21$, I2 = 34%). A fixed-effect model was used to merge SMD values. The pooled data was -0.57 (95% CI: -0.71 to -0.43, Z = 8.91, $P < .00001$; Figure 3), which indicated that there was a statistically significant reduction in UAER in the vitamin D treated group.

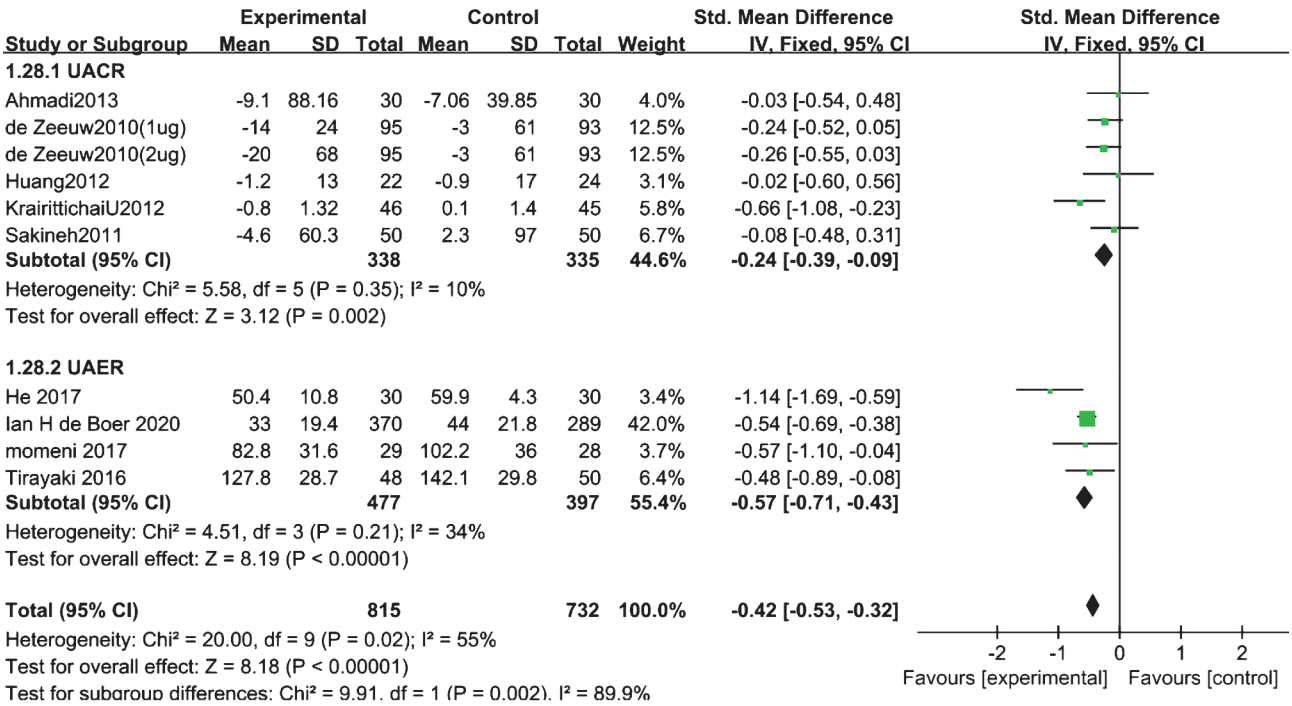

Figure 3. Effect of Vitamin D Supplementation on UACR and UAER

DISCUSSION

Vitamin D plays a vital role in calcium homeostasis and bone metabolism. It has long been used in the treatment of calcium and phosphorus disorders and secondary hyperparathyroidism (SHPT) in CKD and maintenance hemodialysis (MHD) patients. Recent studies suggested that vitamin D can delay the progression of kidney damage in DN patients, probably by ameliorating proteinuria, although many other mechanisms might also be involved.[17] However, other studies could not find a benefit of vitamin D administration, on urinary protein excretion in DN,[18] Considering these controversies, this meta-analysis was performed specifically to evaluate the effect of vitamin D administration on UACR and UAER in patients with DN. Other possible effects of vitamin D on kidneys were not analyzed. A total of nine RCTs were selected and the pooled result supported the current evidence for the clinical benefit of vitamin D to reduce urinary albumin excretion in patients with DN.

The anti-proteinuric effect of vitamin D may have multiple different mechanisms. Firstly, Vitamin D is a negative regulator of the renin-angiotensin-aldosterone system (RAAS), which plays a critical role in the development of DN.[19] It can also inhibit the production of cytokines, such as transforming growth factor-β (TGF-β) and monocyte chemoattractant protein-1 (MCP-1),[20] which have a pivotal role in the progression of glomerulosclerosis. Furthermore, there are studies that have demonstrated the effect of vitamin D on decreasing the progression of renal fibrosis, by inhibiting insulin-like growth factor-1 (IGF-1) and ameliorating podocyte injury, through the nephrin signaling pathway.[22]

Another important factor is insulin resistance, which is not only an important cause of type 2 diabetes mellitus (T2DM) but also the basis for renal injury in T2DM patients. Recent evidence suggests that vitamin D could alleviate insulin resistance.[23,24] The mechanism might be the increased expression of the insulin receptor, promoted by vitamin D. Another study revealed that vitamin D receptors islet beta cells and polymorphism of vitamin D receptor genes (TaqI, BsmI, ApaI, FokI) are closely linked to insulin resistance.

Furthermore, abnormal lipid metabolism is an independent risk factor for DN. Lipid deposition promotes the proliferation of the mesangial cell and the production of extracellular matrix. Lee *et al.* showed that vitamin D inhibits the expression of peroxisome proliferator-activated receptors (PPARs) and the differentiation of 3T3-L1 pre-adipocytes to adipocytes.[25] Other studies have also shown that vitamin D could reduce blood lipids by increasing apolipoprotein A1 and high-density lipoprotein cholesterol.[26]

In addition, micro-inflammation plays a crucial role in the development of DN, which may ultimately lead to fibrosis and glomerular hyalinization. According to an earlier research, vitamin D preparations have anti-inflammatory and immunomodulatory effects, and protect the kidneys by reducing local micro-inflammation.[27,29] Based on the results of another systematic review, vitamin D- treated DN patients had statistically significant reduced levels of serum micro-inflammatory markers, including TNF, IL-6, and CRP.[30]

However, this meta-analysis had several limitations. First of all, our study was confined to the urinary albumin excretion in DN, and the potential effects of vitamin D supplementation on other indices, such as 24-hour urinary protein excretion, kidney function, micro-inflammation and glycemic control, remain to be studied. Moreover, publication bias may have some effect on the results, because the funnel plots of the included studies, seemed to be asymmetrical. Finally, while sensitivity analysis revealed that the results were robust, the accuracy of the pooled results may be influenced by the heterogeneity of the analysis. The inter-study heterogeneity may be due to population diversity, the type and dosage of vitamin D formulations and the different follow-up lengths. Considering these limitations, further multicenter, large-scale and high-quality trials are required in the future.

CONCLUSION

This meta-analysis supports the current evidence for the therapeutic effect of vitamin D in reducing urinary albumin excretion in DN patients. More RCTs are required in the future to assess the effect of vitamin D supplementation on proteinuria and kidney function in DN patients.

AUTHORS' CONTRIBUTIONS

Lei He and Lin Zhou contributed to the study design, data analysis and manuscript. Tian-ya Zhao performed article review. Long Ouyang helped with

the data analysis. Alexander Temple Witherspoon helped with English language proofreading. All authors read and approved the final manuscript.

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