

Review

Vitamin D and diabetic nephropathy: A systematic review and meta-analysis



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ABSTRACT

Objective: There has been a long history documenting the use of different vitamin D derivatives as therapy for renal diseases. However, to our knowledge, there is no comprehensive assessment of the relation between vitamin D deficiency and risk for diabetic nephropathy (DN). Additionally, the effect of vitamin D supplementation on DN is still unclear. The aim of this meta-analysis was to assess these issues by pooling together the results from cross-sectional studies and clinical trials. **Methods:** A systematic literature search of PubMed, Scopus, and Google Scholar was conducted, ending in September 2014. For cross-sectional studies, odds ratio was used as a measure of the association between vitamin D status and risk for DN; for clinical trials, mean and SD of the main outcome (urine albumin-to-creatinine ratio [UACR]) in intervention and placebo groups were considered for analysis.

Results: The final selected articles were published between 2009 and 2014. In all, 3700 and 219 patients were enrolled in observational and interventional studies, respectively. The pooled odds ratio from six cross-sectional studies was 1.80 (95% confidence interval [CI], 1.25–2.59; $P = 0.002$), indicating a significant inverse association between serum vitamin D status and risk for nephropathy in patients with diabetes. However, the pooled data of UACR levels in clinical trials suggested no significant change following vitamin D supplementation (17.98; 95% CI, –35.35 to 71.32; $P = 0.51$).

Conclusion: This meta-analysis showed the higher risk for nephropathy in vitamin D-deficient patients with diabetes. Pooling the results of available clinical trials after vitamin D supplementation did not support causality in this association.

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Introduction

Diabetes mellitus, as one of the most common metabolic disorders in adults, has dramatically increased in prevalence during the past few decades. According to 2013 estimates from the International Diabetes Federation, 382 million people had diabetes, and this number is expected to rise to 592 million by

2035 [1]. In addition to the deleterious effects of the disease itself, its long-term vascular complications, which affect about 40% of individuals with diabetes, can conspicuously decrease quality of life for these patients. Among these complications, diabetic nephropathy (DN), characterized by the development of proteinuria, represents the major cause of end-stage renal failure in Western societies [2]. Some previous studies have shown an inverse association between serum 25-hydroxyvitamin D [25(OH)D] levels and prevalence of diabetes and its complications [3,4], and an improvement of symptoms after vitamin D supplementation [5–7]. These findings can be understood in terms of the role of vitamin D in immunity, β -cell function and insulin sensitivity. Additionally, some cross-sectional

JRS and KD revised the article for important intellectual content. SS performed data analysis and interpretation. HD designed the study and drafted the manuscript. HD and HN reviewed and selected the articles.

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studies showed an association between vitamin D deficiency and DN [8,9].

There is a long history of the use of different vitamin D derivatives in renal disease therapy and some reports have suggested that vitamin D compounds can reduce overall mortality in chronic kidney diseases [10]. There are a number of hypotheses explaining how vitamin D might reverse the progression of DN, such as improving glucose metabolism, minimizing renin-angiotensin system (RAS) activation, and reducing fibrosis [11]. However, this beneficial effect has not yet been clinically demonstrated, and the results of interventional experiments concerning the effect of vitamin D on proteinuria have been inconclusive [12,13]. To our knowledge, at present there is no comprehensive assessment of the relation between vitamin D and DN. Therefore, we conducted this meta-analysis by pooling the results from cross-sectional studies and clinical trials to examine the potential association between vitamin D and DN.

Methods

Literature search

Relevant articles were identified by a systematic search of PubMed, SCOPUS, and Google Scholar through September 2014, using the search terms *vitamin D*, *cholecalciferol*, *calcitriol*, *diabetes mellitus*, *nephropathy*, and *diabetic nephropathies* in the title, abstract, and keywords with no restriction imposed. Additional papers were found through a manual search of reference lists of review articles. The outcome of interest was the urine albumin-to-creatinine ratio (UACR) because proteinuria is considered the main manifestation of nephropathy. Nephropathy was defined as UACR >30 mg/g and vitamin D deficiency was defined as 25(OH) D serum concentration of <20 ng/mL. Initially, we included all cross-sectional studies and controlled randomized clinical trials (RCTs) that evaluated the relationship or effect of vitamin D with or on DN, with no restriction for date, place, and language to maximize the extent of results. Animal experiments, chemistry, or cell-line studies and editorial, commentaries, review articles, and case reports were excluded. Other exclusion criteria consisted of studies without a placebo group, studies using vitamin D derivatives other than D₃, lack of relevant data, lack of precise data needed for our analysis, and using indices other than UACR for diagnosis of nephropathy. Two independent reviewers (H.D. and H.N.) reviewed all titles and abstracts to ascertain whether the studies met our criteria to be eligible for analysis. The full texts of selected articles were then considered to extract information. The quality assessment for each article was made based on specific criteria outlined in the Newcastle–Ottawa Scale (NOS) adapted for cross-sectional studies and the Oxford quality scoring system (Jadad score) for clinical trials [14,15].

Data extraction

Data extracted from the selected articles included last name of first author, publication year, location of study, study population and design, season, sample size, subject characteristics (type of diabetes, age, sex), dose and duration of intervention, 25(OH)D assay methods, type of vitamin D supplement, 25(OH)D concentration, 25(OH)D cutoff, UACR and odds ratio (OR) (with corresponding 95% confidence interval [CI]). In the case of relevant missing data, contacts were made to the main authors for more information.

Statistical analysis

For cross-sectional studies, the OR was used as a measure of the association between vitamin D status and risk for DN, and for clinical trials mean and SD of the main outcome in intervention and placebo groups were considered for analysis. To examine statistical heterogeneity across studies a χ^2 test was used on (n-1) degrees of freedom. The percentage of $I^2 < 25$, near 50, and >75 indicated low, moderate, and high heterogeneity, respectively [16]. Either a fixed-effects model or, in the presence of heterogeneity, a random-effects model was used to combine the study results. Potential publication bias was assessed by the two formal tests of Begg and Egger [17,18]. All analyses were performed using STATA statistical software (Version 12.0, Stata Corporation, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

We identified 613 studies. In the first round of screening, 299 articles remained after excluding duplicates. We excluded 267

studies for one of the following reasons: irrelevant data; not including our main exposure, that is, circulating 25(OH)D or main outcome (UACR); non-human experimental articles; chemistry or cell-line studies; editorial, commentaries, review articles, and case reports. In the second round, full-text articles were retrieved (n = 32), 22 articles were excluded for inadequate data, and finally four clinical trials [19–22] and six cross-sectional studies [19,23–27] were identified as eligible for inclusion in the meta-analysis (Fig. 1; Tables 1 and 2).

Study characteristics

The final selected articles were published between 2009 and 2014. In all, 3700 and 219 patients were enrolled in observational and interventional studies, respectively. Participants were selected from different countries (United States, China, India, Thailand, Slovakia, Iran, and Malaysia) with an age range of 9 to 75 y. The six cross-sectional studies investigated the relationship between vitamin D deficiency and DN, whereas the four clinical trials examined whether vitamin D supplementation could improve proteinuria in patients with DN. With the exception of three cross-sectional studies, other experiments only included type 2 diabetes. The characteristics of studies are briefly presented in Tables 1 and 2.

Association between vitamin D deficiency and risk for DN

The ORs from six cross-sectional studies varied from 0.35 to 4.1. Five of the six studies reported a significant higher risk for nephropathy in vitamin D-deficient adults with diabetes, whereas one study, which enrolled only adolescents with type 1 diabetes, found no significant association. The pooled OR was 1.80 (95% CI, 1.25–2.59; $P = 0.002$; Fig. 2). Because I^2 of 59% indicated a moderate heterogeneity, we explored the potential source by subgroup analysis and found that age of participants was a significant modifier. Only one study, which included adolescents, reported an inverse association between proteinuria and vitamin D deficiency. The Egger's and Begg's test did not provide evidence for publication bias ($P = 0.85$ and $P = 0.58$, respectively).

Effects of vitamin D supplementation on DN

Four RCTs (comprising 219 patients) compared the effects of vitamin D₃ supplementation versus placebo on proteinuria in nephropathic patients. The pooled data of UACR levels in different studies suggested no significant change after vitamin D intake (17.98; 95% CI, –35.35 to 71.32; $P = 0.51$; Fig. 3). I^2 value, Begg's and Egger's tests suggested no heterogeneity ($P = 0.62$) or publication bias ($P = 0.70$ and $P = 0.80$, respectively).

Discussion

The results of this meta-analysis showed a higher risk for DN in vitamin D-deficient patients. Some existing evidence suggests that vitamin D deficiency might be a prominent feature of chronic kidney disease and this vitamin hormone has renoprotective activity. Although it has been prescribed for renal patients to prevent osteodystrophy since the middle of the 20th century, its extraskeletal role in metabolism, immunity, and inflammation has received more attention in the past few decades [28]. The vitamin D receptor is highly expressed in the kidney; therefore, the kidney can be considered a classic vitamin D target organ. In the Third National Health and Nutrition Examination Survey, an

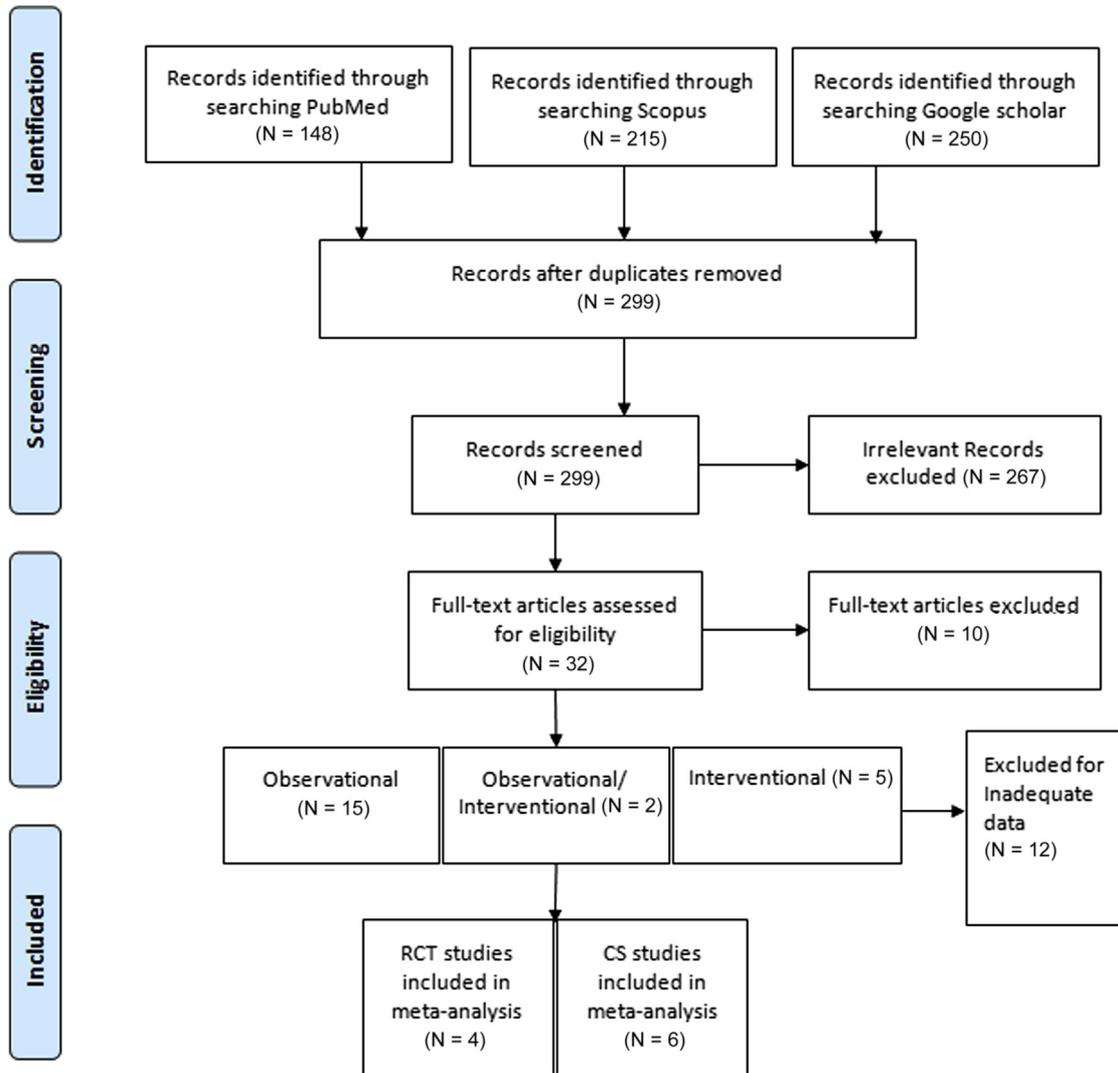


Fig. 1. Literature review and study selection. CS, cross-sectional; RCT, randomized control trial.

inverse association was reported between the prevalence of albuminuria and serum 25(OH)D concentration [29]. Since then, several studies investigated the relationship between vitamin D status and DN, of which we included six cross-sectional studies in our meta-analysis. The estimated pooled OR of 1.80 indicated the higher risk for DN with vitamin D deficiency. However, these association studies did not show causality.

Our analysis of the clinical trials showed no significant effect of vitamin D intake on nephropathy. However, only a few clinical trials have been conducted to evaluate whether vitamin D therapy is beneficial in DN. We included only four studies in our meta-analysis and the pooled effect of vitamin D supplementation on UACR was not statistically significant. There are some other well-designed experiments in this field

Table 1
Characteristics of cross-sectional studies Involved in meta-analysis

Study (y)	Country	Study population	Type of diabetes	Sample size (male %)	Vitamin D assay	Vitamin D deficiency cutoff (ng/mL)	Overall vitamin D level (ng/mL)	Nephropathy cutoff (UACR mg/g)	OR
Diaz (2009)	US	Adult	1 and 2	1216 (48)	Chemiluminescent immunoassay	20	20.6	30	1.85
Huang (2012)	China	Adult	2	559 (59)	Chemiluminescent immunoassay	20	Not mentioned	30	1.65
DeBoer (2012)	US	Adult	1	1193 (53)	HPLC	20	25.4	30	1.63
Vojtkova (2012)	Slovakia	Adolescent	1	58 (52)	Elecsys	20	27.2	30	0.35
Li (2013)	China	Adult	2	594 (not mentioned)	Not mentioned	20	Not mentioned	30	1.78
Bajaj (2014)	India	Adult	2	158 (60)	Not mentioned	20	19.0	30	4.09

HPLC, high-performance liquid chromatography; UACR, urine albumin-to-creatinine ratio

Table 2
Characteristics of clinical trials Involved in meta-analysis

Study (y)	Country	Study population	Sample size (total)	Type of diabetes	Mean age	Supplement form and dosage	Duration of intervention (wk)	Baseline vitamin D in case vs control (ng/mL)	Final vitamin D in case vs control (ng/mL)	Comparing final proteinuria in case and control groups
Huang (2012)	China	Diabetic + Nephropaty + D deficient	46	2	60	Cholecalciferol 800 IU/d	24	14.4 vs. 13.4	17.5 vs. 10.5	No significant difference ($P = 0.23$)
Krairitichai (2012)	Thailand	Diabetic + Nephropaty + D deficient	91	2	57	Calcitriol 20 IU/bid	16	Not mentioned	Not mentioned	Significant difference ($P = 0.01$)
Ahmadi (2013)	Iran	Diabetic + Nephropaty + D deficient	51	2	58	Cholecalciferol 50 000 IU/wk	12	14 vs. 16	71.2 vs. 17.6	No significant difference ($P = 0.91$)
Mustafar (2013)	Malaysia	Diabetic + Nephropaty + D deficient	31	2	57	Calcitriol 20 IU/d	6	14.4 vs. 16.2	18 vs. 19	No significant difference ($P = 0.46$)
Mustafar (2013)	Malaysia	Diabetic + Nephropaty + D deficient	31	2	57	Calcitriol 20 IU/d	12	14.4 vs. 16.2	19 vs. 21	No significant difference ($P = 0.64$)

that were excluded from our analysis because of study design or because they used vitamin D analogs. Namely, the VITamin D and Omega-3 Trial (VITAL) study investigated an active vitamin D analog (paricalcitol) in patients with DN who were being treated with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. After a 24-wk intervention, 2 $\mu\text{g}/\text{d}$ of paricalcitol decreased albumin excretion significantly compared with the placebo group [13]. Another study measured urinary albumin, monocyte chemoattractant

protein-1 and transforming growth factor (TGF)- β 1 before and after intervention with vitamin D and found that increases in serum vitamin D level correlated with a decrease in UACR and TGF- β 1 [30]. In contrast, another group of researchers reported that 0.5 $\mu\text{g}/\text{d}$ calcitriol for 8 wk did not significantly affect the albumin excretion rate [31]. It should be noted that the major limitation in the clinical use of vitamin D supplements in nondialyzed patients is the risk for hypercalcemia as a result of deterioration in normal renal function.

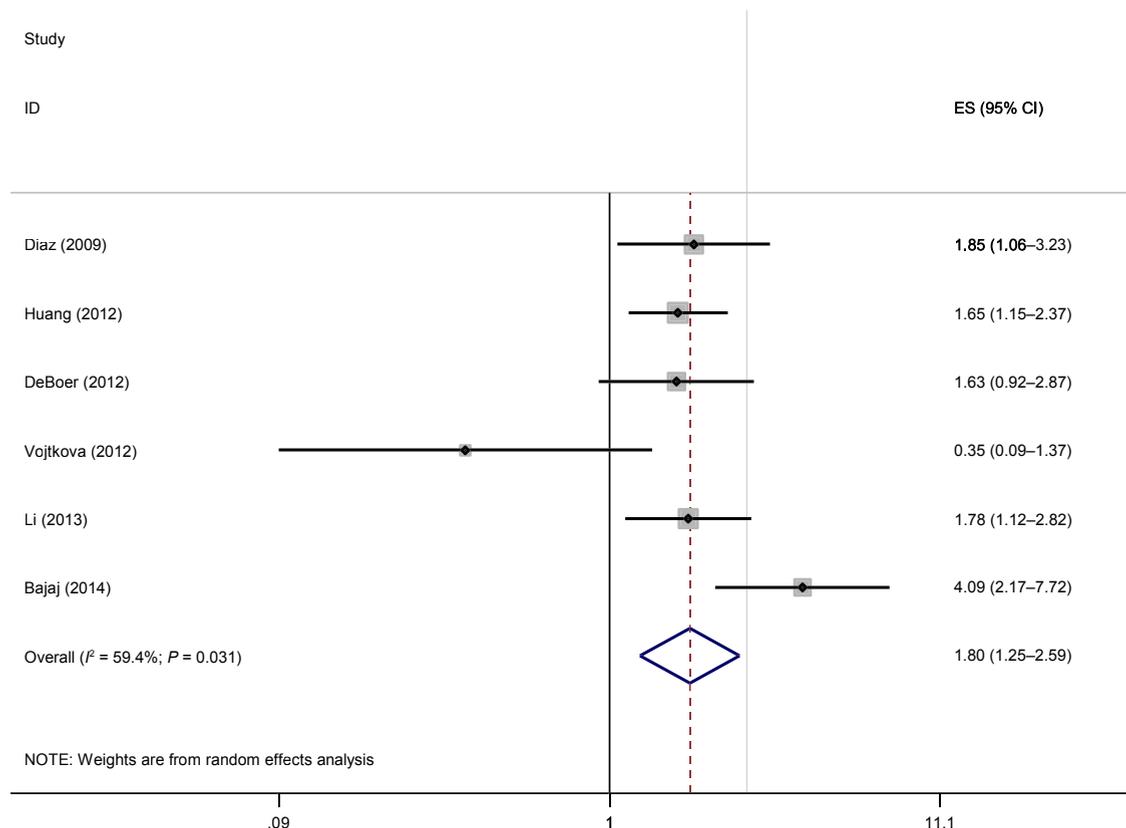


Fig. 2. Evaluation of the risk for diabetic nephropathy (urine albumin-to-creatinine ratio >30 mg/g) in vitamin D-deficient [serum 25(OH)D <20 ng/mL] patients with diabetes; meta-analysis of six cross-sectional studies.

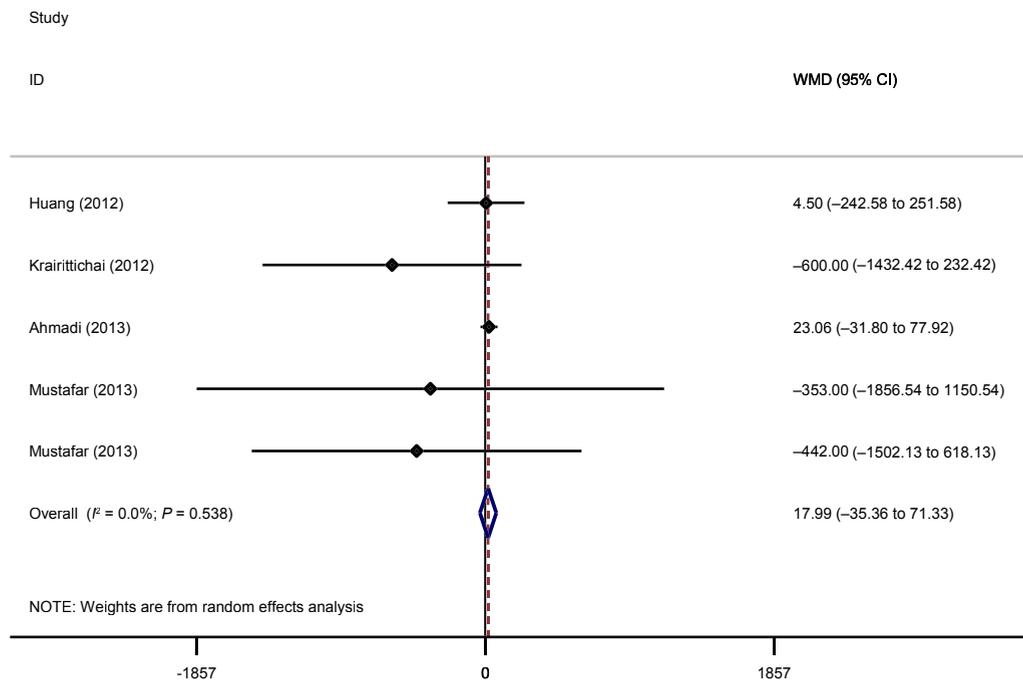


Fig. 3. Evaluation of the effect of vitamin D supplementation on urine albumin to creatinine ratio in patients with diabetes; meta-analysis of four clinical trials.

The underlying mechanisms for the cross-sectional relationship between vitamin D and DN remain unclear. Some animal studies showed that knockout of the vitamin D receptor in diabetic mice was associated with severe albuminuria and glomerulosclerosis [32]. Alternatively, vitamin D might slow the progression of DN by improving insulin secretion, delaying destruction of β -islet cells, affecting osteocalcin and consequently assisting in glucose metabolism [4,33,34]. In addition, $1,25(\text{OH})_2\text{D}_3$ is known as a RAS inhibitor due to its negative regulatory effect on renin production [35]. TGF- β , MCP-1, hepatocyte growth factor, thrombospondin-1, and plasminogen activator inhibitor are other possible molecular targets of vitamin D action [36–38]. Needless to say, renal disease might also alter vitamin D metabolism. For instance, cytochrome P450 (CYP)27B1, the enzyme that converts $25(\text{OH})\text{D}_3$ to the active hormone, decreases and CYP24A1, the enzyme that catabolize $1,25(\text{OH})_2\text{D}_3$ and $25(\text{OH})\text{D}_3$, increases in the kidneys of individuals with diabetes [39,40]. The decline in vitamin D levels might also be due to urinary excretion of vitamin D-binding proteins cubilin, and megalin, which are important proteins in vitamin D homeostasis [41,42].

In conclusion, this meta-analysis of the six cross-sectional studies indicated a higher risk for nephropathy in vitamin D-deficient patients with diabetes. However, pooling the results of available clinical trials showed no significant change in proteinuria after vitamin D supplementation. The strength of this meta-analysis was the inclusion and comparison of both observational and interventional studies. The main limitation was the lack of access to complete data of all related published papers, despite correspondence to the authors. We included studies in which cholecalciferol and calcitriol were administered, so the effect of other vitamin D analogs might be different. Additionally, the number of patients in these studies was quite small, and in some cases the serum vitamin D had not elevated conspicuously after the supplementation. This may affect the interpretation of the results. Further clinical trials on different forms and doses of

vitamin D are needed for a more comprehensive and precise conclusion.

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