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Role of vitamin D in the development and progression of diabetic kidney disease: an overview of meta-analyses

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Abstract

Background: The effectiveness of vitamin D supplementation in the progression of diabetic kidney disease (DKD) remains controversial. Our review tries to provide a comprehensive summary of all the relevant articles in the area to assess the association of vitamin D deficiency with the development of DKD and the effect of vitamin D supplementation on the progression of DKD.

Methods: PubMed, Embase, Scopus, Cochrane Library and Web of Science were accessed from inception till June 2024 to obtain all the relevant meta-analyses assessing the function of vitamin D in the onset and prognosis of DKD. The summary data were extracted by two independent reviewers. A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2 tool was used for the assessment of the methodological quality of the included meta-analyses.

Results: A total of 4579 articles were obtained from 5 databases in the initial search, of which 8 meta-analyses were included for the evidence synthesis. The methodological quality of the retrieved articles ranged from critically low to high. Serum vitamin D levels were significantly correlated with the prevalence of DKD. The review suggested that vitamin D supplementation could help in reducing proteinuria. However, no such changes were observed in other renal function parameters of DKD patients following vitamin D supplementation.

Conclusion: The current evidence indicates that vitamin D supplementation could be beneficial in reducing proteinuria among DKD patients.

PROSPERO registration number: CRD42022375194.

Plain language summary

Role of vitamin D in diabetic kidney disease: overview of meta-analyses

Vitamin D is a steroid hormone synthesized in the skin through exposure to sunlight and is believed to play a role in diverse conditions such as diabetes, thyroid disorders, and cancer. Recent studies suggest that vitamin D deficiency may be linked to the development of diabetic kidney disease (DKD). However, clinical trials investigating the effect of vitamin D supplementation on the progression of diabetic kidney disease have produced conflicting results. To clarify these findings, we conducted an overview of meta-analyses to summarize all the existing evidence on the role of vitamin D in the development and progression of DKD. The study, conducted through June 2024, reviewed eight meta-analyses that met our eligibility criteria, which included meta-analyses of either randomized controlled trials (RCTs) or observational studies. The results of this overview indicate that vitamin D deficiency is associated with DKD as per the meta-

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analyses of observational studies. In contrast, meta-analyses of RCTs suggest that while vitamin D supplements may help reduce proteinuria, it has no significant impact on other measures of kidney function. This lack of evidence may be due to various factors, such as variations in the dose, dosage, duration and type of vitamin D supplement used across studies. Furthermore, the appropriate dose, frequency, and duration for effective treatment remain unclear. Therefore, there exists a critical need to identify the optimal dosage and duration of vitamin D required to reduce the progression of DKD with respect to the stage of DKD. In conclusion, this overview suggests that vitamin D may have a role in DKD, offering valuable insights into its therapeutic potential and highlighting potential avenues for further research on its dosage optimization management of DKD.

Keywords: diabetic kidney disease, evidence-based medicine, systematic review, vitamin D

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Introduction

Diabetes mellitus (DM) has become a global scourge, affecting millions yearly. The incidence of diabetes has increased from 11.3 million in 1990 to 22.9 million in 2017, representing a 102% rise.[1] Diabetes poses a substantial threat as it can increase the economic burden and significantly decrease the quality of life. Approximately 20%–40% of diabetic patients develop diabetic kidney disease (DKD), which is thought to be responsible for around 80% of all cases of end-stage renal disease.[2] DKD is also associated with higher mortality rates and a huge financial burden among diabetes patients.[3,4]

Vitamin D, a nutritional supplement, is currently being investigated for its potential association with DKD. It is a secosteroid synthesized in the skin upon sun exposure and can also be obtained from the diet, including fortified foods, fortified dairy products and fatty fish. Since dietary sources provide only small amounts of vitamin D, sun exposure is often considered its primary source.[5–7] Once synthesized or ingested, vitamin D undergoes hydroxylation in the liver to form 25-hydroxyvitamin D (25(OH)D), the major circulating form. It is then further hydroxylated in the kidneys to form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the biologically active form. This active form binds to the vitamin D receptor, which is a family of nuclear hormone receptors, to exert its diverse physiological effects.[8,9] Vitamin D, a nutritional supplement, is currently being investigated for its potential association with DKD. Recent studies suggest that vitamin D deficiency might play a role in renal damage among diabetics.[10–12] The potential mechanism behind this may involve the interplay between the vitamin D receptor and the transcription-5 signalling pathway, which could mediate this anti-inflammatory and immunomodulatory activity. Additionally, vitamin D acts as an inhibitor of the renin-angiotensin-aldosterone system (RAAS). When vitamin D levels decrease, RAAS gets activated, leading to nephropathy.[13] According to estimates, diabetics with chronic kidney disease (CKD) exhibited a 1.7-fold higher vitamin D insufficiency than those without CKD.[14] In addition, serum 25(OH) vitamin D levels below 15 ng/ml in DKD have been linked to a faster reduction in the estimated glomerular filtration rate (eGFR) than in those with 25(OH) vitamin D levels over 15 ng/ml.[15] Moreover, a 53% higher risk of mortality was observed in CKD stages 3 and 4 patients with 25(OD) vitamin D levels lesser than 15 ng/ml.[16]

A strong association has been demonstrated by observational studies between vitamin D deficiency and DKD.[17–21] However, the outcomes of interventional studies on this topic are still subject to debate. While some of the interventional studies reported that vitamin D reduces the progression of DKD,[22–24] others could not find a significant benefit.[25–27] As a result, the clinical significance of vitamin D supplementation in the development and progression of DKD remains uncertain.

Systematic reviews and meta-analyses are regarded as the most robust form of evidence in the hierarchy of evidence-based medicine.[28] Existing meta-analyses cannot provide consistent results concerning the association between vitamin D and DKD. Zhao et al.[29] and Wang et al.[30] reported that vitamin D supplements could significantly reduce proteinuria, but other meta-analyses could not identify such an association.[31,32] Therefore, this study aimed to conduct an overview of all available meta-analyses on vitamin D and its role in DKD to summarize the association between vitamin D deficiency and the development of DKD as well as the effects of vitamin D supplementation DKD progression.

Methodology

To perform this overview of meta-analyses, we complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[33] and a PE/ICOS (Participants, Exposure/Intervention, Comparator, Outcome and Study design) framework was adopted for the inclusion of studies. Before initiating the study, a detailed protocol was registered in PROSPERO (CRD42022375194).

Literature search

A comprehensive literature search was done on databases such as PubMed, Scopus, Embase, Web of Science and Cochrane Library to obtain all relevant meta-analyses published from inception to June 2024. Key terms such as Vitamin D, Diabetic Nephropathy and Diabetic kidney disease, along with their equivalent MeSH terms, were used to define the search strategy (File S1). A bibliographical search was conducted in all the incorporated studies to find additional relevant studies.

Criteria for selection of studies

Population. Type 1 or type 2 DM patients with DKD as population was included in the study. DM should be diagnosed according to WHO's diagnostic criteria for diabetes.[34] DM with any other comorbidities or complications was excluded.

Intervention/exposure. Studies used vitamin D deficiency or supplementation as an exposure, and 25(OH) vitamin D levels as an indicator were included. According to the author's discretion, the terms vitamin D deficiency and insufficiency were defined.[35] No restrictions were applied for the type of supplement used, dose, dosing interval, route of administration or duration of treatment.

Comparator. Normal vitamin D level was considered as the comparator against vitamin D deficiency in studies investigating the etiological association with DKD. In interventional studies, vitamin D supplementation was compared against a placebo, active comparator, or no treatment to assess the prognosis of DKD patients at the authors' discretion.

Outcome. Primary outcomes include the association of vitamin D deficiency with the development of DKD, and the progression of DKD following vitamin D supplementation, which was evaluated using a change in proteinuria levels and renal function. Proteinuria is assessed based on 24-h urine protein, urine albumin excretion ratio (UAER) and urine albumin creatinine ratio (UACR).[36] Serum creatinine (SCr) and eGFR were used to assess renal function.[37] The secondary outcomes of the study include the change in glycaemic control, serum calcium and vitamin D levels.

Study design. The meta-analyses examining the association between vitamin D and the development or prognosis of DKD were included. Studies available only in English languages were considered as the authors were familiar with English. We excluded all primary research and systematic reviews without a meta-analysis.

Study selection and data extraction

Initially, each retrieved article was title and abstract-screened in accordance with the eligibility criteria. Eligible studies identified during the initial screening were retrieved in full text and assessed for inclusion as per the predefined inclusion criteria. The relevant data, including the author, publication year, the number of primary studies included, study characteristics, PI/ECOS, quality of studies included, summary effect estimates with corresponding 95% confidence intervals (CIs), a measure of inconsistency among the included studies (I^2), publication bias, risk of bias were collected. Two independent reviewers (A.C. and M.R.) were involved in the screening of the articles and data extraction. Any disagreements were settled through consensus or consultation

with a third reviewer (S.R.R./G.T.). In the case of missing data, the authors of primary studies were contacted through email.

While some of the meta-analyses did not provide information on the risk of bias, we assessed the essential features of methodological quality at the meta-analysis level. The risk of bias assessment at the level of included studies was beyond the scope of this review.

Quality assessment of meta-analysis

The online version of the A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2 checklist (https://amstar.ca/Amstar_Checklist.php) was used by two independent reviewers (A.C./M.R.) to evaluate the methodological quality of included meta-analyses.[38] The quality of meta-analyses were then graded as either critically low, low, moderate or high. Any differences in the opinion were sorted out through consensus or consultation with a third reviewer (P.G.P./G.T.).

Evidence synthesis

The evidence from the included meta-analyses was narratively synthesized and presented in a tabular format and classified as per outcomes. The continuous outcomes were reported as standardized mean difference (SMD) or weighted mean difference with 95% CI, while categorical outcomes were reported as odds ratios (ORs) with 95% CI. The outcomes were then categorized based on the type, dosage and duration of vitamin D, as per data availability.

Results

Literature search

Of the 4579 articles retrieved in the initial search, 3883 were title and abstract screened after the elimination of 696 duplicates. From them, 229 underwent full-text screening resulting in the identification of 8 meta-analyses that met the inclusion criteria. The study selection process is mentioned in the PRISMA flowchart (Figure 1). The reasons for the exclusion of each article during full-text screening are provided in File S2.

Study characteristics

An overview of the characteristics of meta-analysis included in this review is provided in Table 1. Among the eight meta-analyses obtained, one was a meta-analysis of observational studies,[39] six were meta-analyses of randomized controlled trials (RCTs)[29,30,32,40–42] and one meta-analysis included both observational studies and RCTs.[31]

The meta-analyses of RCTs investigated the effect of vitamin D supplements on the progression of DKD. The vitamin D analogues examined in the primary studies included cholecalciferol, calcitriol, paricalcitol and alfacalcidol, either administered alone or in combination with active treatments such as angiotensin-receptor blockers (ARBs). A total of 3952 participants were included, with a median of 1046 participants per meta-analysis. In total, 47 primary studies were involved, most of which were in Chinese and could not be retrieved, thus, precluding a detailed analysis of these primary studies.

The meta-analyses of observational studies assessing the relationship between vitamin D deficiency and DKD development which was determined based on the presence of either microalbuminuria or macroalbuminuria. The included primary studies were predominantly cross-sectional, comprising a total population of 3044 participants across 7 studies.

Methodological quality

The AMSTAR 2-based methodological quality of the included meta-analyses varied from critically low to high. Among the eight meta-analyses, three were deemed high quality,[29,30,32] one deemed moderate quality,[40] one deemed low quality[41] and three deemed critically low quality.[31,39,42] Major reasons for the loss of quality of the articles were the lack of assessment of potential risks of bias of individual studies and its impact on interpreting results, as well as inadequate explanation for the heterogeneity observed in the pooled results. Overall AMSTAR 2 findings are described in Table 1, and the detailed description is given in File S3.

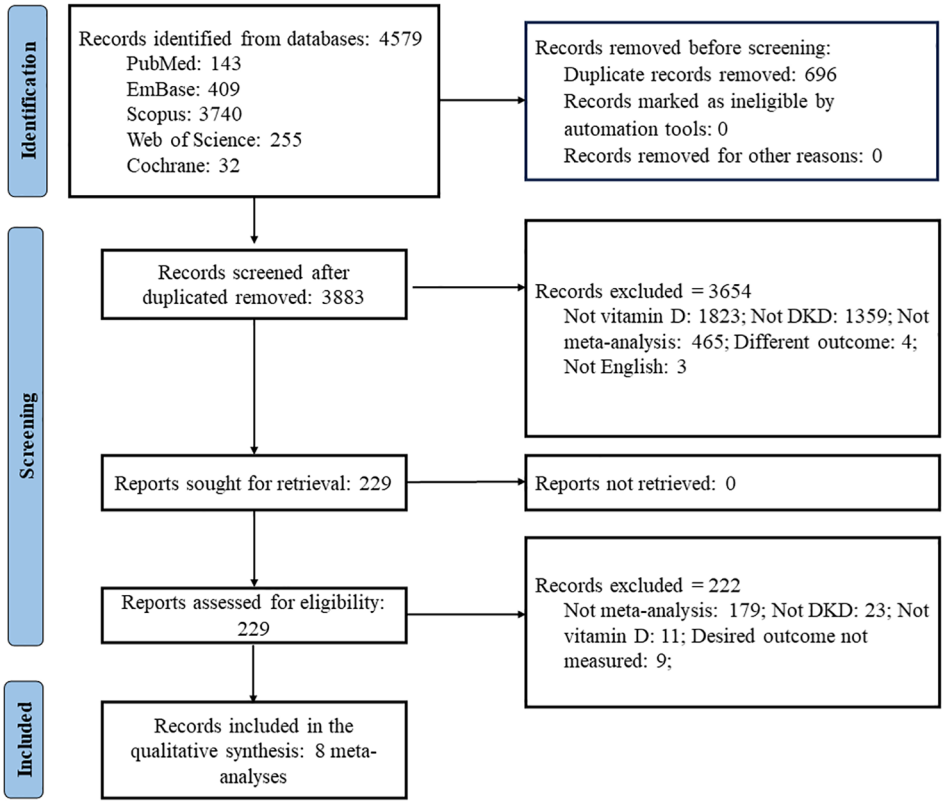

Figure 1. PRISMA flowchart.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Association between vitamin D deficiency and the development of DKD

Two meta-analyses reviewed the interaction between vitamin D deficiency and DKD development, both demonstrating significant associations.[31,39] Derakhshanian et al.[31] included 6 studies totalling 3700 participants and found an association (OR = 1.80 (1.25–2.59)). Fang et al.[39] included only one study and reported a significant association (OR = 4.06 (2.11, 7.78); Table 2).

Effect of vitamin D supplementation on 24-h urine protein

All four meta-analyses observed a reduction in 24-h urine protein levels following vitamin D supplementation.[29,30,41,42] Significant heterogeneity was observed in three of the meta-analyses.[29,30,42] Variation in the geographical regions and the evidence of ARBs/ACEIs being stopped 1 month before trial in a few studies could be the possible source of this heterogeneity. The AMSTAR-2-based methodological quality ranged from high[29,30] to low[41] to critically low quality[42] (Table 2).

Subgroup analyses were done in three meta-analyses with respect to the type of vitamin D analogue used, placebo-controlled versus active-controlled trials, and the dose and duration of calcitriol. It was found that active-controlled trials showed a better reduction in the 24-h urine protein levels post-supplementation (MD 0.49 (−0.72, −0.26), $p < 0.0001$ vs −0.15 (−0.23, −0.06), $p < 0.001$).[42] Additionally, significant reductions were observed with smaller doses (<0.25 µg/day; MD −0.19 (−0.36, −0.01), $p = 0.02$ vs MD −0.31 (−0.44, −0.19), $p = 0.10$) and with long-term calcitriol (4–6 months; MD −0.31 (−0.44, −0.19), $p < 0.00001$ vs MD −0.19 (−0.36, −0.01), $p = 0.02$).[30]

Effect of vitamin D supplementation on UACR

Four out of five meta-analyses indicated that UACR levels reduced following vitamin D supplementation,[29,32,40,42] except Derakhshanian et al.[31] Notably, Derakhshanian et al.[31] had a considerably smaller sample size (219) compared to others (more than 450). Additionally, the study

Table 1. Characteristics of the meta-analyses included.

Author (year)[Ref.]	Countries included in the review	Number of studies; total participants (I/C)	Study period	Appraisal tool used	Funding source	Egger's *p*-value	AMSTAR rating
Meta-analyses of randomized controlled trials							
Zhao et al. (2014)[29]	China, Germany, Greece, Iran, Italy, Netherlands, Poland, Portugal, Spain, Taiwan, Thailand and the United States	20; 1497 (797/700)	Inception to January 2014	Cochrane risk of bias assessment tool	Natural Science Fund of Shandong Province (No. Y2006C76), Fund for the Returned Oversea Scholars Sponsored by National Ministry of Personnel (2008, No. 102), Grant for Excellent Young and Middle-aged Scientists of Shandong Province (No. 2004BS02016)	NR	High
Derakhshanian et al. (2015)[31]	China, Iran, Malaysia and Thailand	4; 219	Inception to September 2014	Oxford quality scoring system (Jadad score)	None	0.8	Critically low
Zhang et al. (2017)[42]	China, Denmark, Germany, Greece, Iran, Italy, Malaysia, Netherlands, Poland, Portugal, Spain, Taiwan, Thailand, Turkey and the United States	24; 1978	Inception to January 2017	NOS	NR	>0.05	Critically low
Wang et al. (2019)[30]	China, Iran, Malaysia, Thailand and Turkey	20; 1464 (732/732)	September 2007 to July 2018	Cochrane risk of bias assessment tool	New Xiangya Talent of Third Xiangya Hospital of Central South University (No. 20160309), the Fundamental Research Funds for the Central Universities of Central South University (No. 1053320180493)	Publication bias except HbA1c, but *p* value was NR	High
Gupta et al. (2019)[32]	China, Germany, Greece, Iran, Italy, Malaysia, Netherlands, Poland, Portugal, Sri Lanka, Spain, Taiwan, Thailand and the United States	9; 734 (369/365)	Inception to January 2018	Cochrane risk of bias assessment tool	None	>0.05	High
Xuan et al. (2023)[41]	China, Iran and Sri Lanka	10; 651 (335/316)	Inception to December 2019	Cochrane risk of bias assessment tool	National Basic Research Program of China: Study on identification of vital energy and spirit in TCM health status (number: 2011CB505406)	NR	Low
He et al. (2022)[40]	China, Germany, Greece, Iran, Italy, Netherlands, Poland, Portugal, Spain, Taiwan, Thailand, Turkey and the United States	9; 1359 (720/639)	Inception to 2022	Cochrane risk of bias assessment tool	NR	Funnel plot suggested publication bias, but *p*-value was NR	Moderate
Meta-analyses of observational studies							
Derakhshanian et al. (2015)[31]	China, India, Slovakia and the United States	6; 3700	Inception to September 2014	NOS	None	0.85	Critically low
Fang et al. (2021)[39]	China	1	Inception to April 2020	NOS	2019 (Fujian) Provincial Health Youth Research Project Funding Program. 2019-1-78	NR	Critically low

AMSTAR, A Measurement Tool to Assess Systematic Reviews; HbA1c, glycated haemoglobin; NOS, Newcastle-Ottawa scale; NR, not reported.

did not provide any information on the risk of bias of included studies or the presence of publication bias and was rated as critically low quality according to AMSTAR-2. In contrast, the analyses showing a reduction in the UACR levels were rated from critically low[42] to moderate[40] to high quality[29,32] according to AMSTAR-2 (Table 2).

Zhang et al.[42] reported significant heterogeneity in the pooled results, ($I^2 = 84.4$, $p = 0.0001$). Potential sources of this heterogeneity include the inclusion of both placebo-controlled and active-controlled trials in the analysis and the variation in the duration of vitamin D supplementation across studies.

Effect of vitamin D supplementation on UAER

Insufficient data exists to substantiate the theory that vitamin D supplementation could reduce UAER levels. The outcome was evaluated in three meta-analyses of RCTs, which indicated a potential reduction in UAER levels in patients with DKD.[30,32,40] However, the findings of Gupta et al.[32] were not statistically significant ($p = 0.14$) and had a smaller sample size (326) when compared to other meta-analyses (more than 650) (Table 2). Although the findings of Wang et al.[30] and He et al.[40] were significant, there was suspected publication bias as there was asymmetry in the funnel plot findings.

Additionally, substantial heterogeneity was observed in the pooled analysis by Wang et al.[30] and Gupta et al.,[32] which could probably be attributed to the variation in the type and duration of vitamin D supplementation. The subgroup analysis by Wang et al.[30] showed that long-term calcitriol (4–6 months) led to a greater reduction in UAER compared to short-term calcitriol supplementation (2–3 months; MD −100.01 (−171.65, −46.37), $p < 0.0001$ vs MD −30.11 (−60.17, −0.05), $p < 0.0001$).[30]

Effect of vitamin D supplementation on SCr

Four meta-analyses assessed the effect of vitamin D on SCr, reporting a reduction from baseline following supplementation; however, this reduction was not statistically significant, except for Xuan et al.[41] Nonetheless, Xuan et al., had a smaller sample size (99), a moderate risk of bias, suspected publication bias and a low AMSTAR-2 quality, indicating uncertainty in the evidence provided.

Considerable heterogeneity was observed in the results of Gupta et al.[32] ($I^2 = 57\%$, $p \leqslant 0.00001$), potentially due to variations in the type of vitamin D analogue used and the smaller sample size. The quality, as assessed by the AMSTAR-2, also varied from high[30,32] to low[41] and critically low[42] (Table 2).

Effect of vitamin D supplementation on eGFR

eGFR levels were found to be increased following vitamin D supplementation (MD = 2.13 (−2.06, 6.32), $p = 0.32$), as reported by Wang et al.[30] The presence of a moderate risk of bias in the studies included and suspected publication bias could be a possible reason for the lack of statistical significance (Table 2).

Effect of vitamin D supplementation on glycaemic control

Vitamin D supplementation in DKD demonstrated little to no difference in the glycaemic control. Four meta-analyses reviewed the effectiveness of vitamin D supplementation on glycated haemoglobin (HbA1c) in DKD and found no significant reduction.[29,30,41,42] There was evidence of the risk of bias in all studies except for that by Xuan et al.[41] Similarly, Wang et al. showed no effect on fasting blood glucose levels following vitamin D supplementation (MD = −0.05 (−0.29, 0.20)[30]; Table 2).

Effect of vitamin D supplementation on serum calcium and vitamin D levels

Vitamin D levels were significantly elevated following supplementation, as evaluated by two meta-analyses.[32,41] However, there exists moderate heterogeneity in the findings, which might have arisen due to the difference in the vitamin D analogues used and variations in the duration of treatment among the primary studies. However, this elevation appears to have little to no effect on serum calcium levels. Two meta-analyses assessed the change in calcium levels following vitamin D supplementation and found a slight elevation, which was not statistically significant[32,42] (Table 2).

Table 2. Summary statistics of included meta-analyses.

Outcome	Author (year)[Ref.]	No. of studies (population)	Type of metrics	Summary effect (95% CI)	I^2	*p*-Value
Association of vitamin D deficiency with DKD	Derakhshanian et al. (2015)[31]	6 (3700)	OR	1.80 (1.25, 2.59)	59.4	0.031
	Fang et al. (2021)[39]	1	OR	4.06 (2.11, 7.78)	–	<0.05
Effect of vitamin D supplementation on 24-h urine protein	Zhao et al. (2014)[29]	5 (329)	WMD	−0.44 (−0.54, −0.34)	52	<0.00001
	Wang et al. (2019)[30]	11 (816)	WMD	−0.26 (−0.34, −0.17)	95	<0.00001
	Xuan et al. (2023)[41]	3 (229)	WMD	−180.92 (−212.67, −149.16)	35	<0.001
	Zhang et al. (2017)[42]	14 (1118)	WMD	−0.23 (−0.30, −0.15)	96.3	<0.0001
Effect of vitamin D supplementation on UACR	Zhao et al. (2014)[29]	4 (454)	SMD	−0.29 (−0.48, −0.10)	8	0.003
	Derakhshanian et al. (2015)[31]	4 (219)	WMD	17.98 (−35.35, 71.32)	0	0.51
	Gupta et al. (2019)[32]	4 (524)	WMD	−0.17 (−0.34, 0.01)	0	0.06
	He et al. (2022)[40]	5 (673)	WMD	−0.24 (−0.39, −0.09)	10	0.002
	Zhang et al. (2017)[42]	6 (592)	SMD	−0.49 (−0.90, −0.08)	84.4	0.0001
Effect of vitamin D supplementation on UAER	Wang et al. (2019)[30]	8 (676)	WMD	−67.36 (−91.96, −42.76)	97	<0.00001
	Gupta et al. (2019)[32]	2 (326)	WMD	−0.18 (−0.43, −0.06)	65	0.14
	He et al. (2022)[40]	4 (874)	SMD	−0.57 (−0.71, −0.43)	34	<0.00001
Effect of vitamin D supplementation on serum creatinine	Wang et al. (2019)[30]	9 (560)	WMD	−0.83 (−3.67, 2.02)	0	0.57
	Gupta et al. (2019)[32]	3 (176)	WMD	−0.15 (−0.62, 0.2)	57	0.53
	Xuan et al. (2023)[41]	3 (99)	WMD	−17.13 (−27.88, −6.37)	0	0.002
	Zhang et al. (2017)[42]	9 (587)	WMD	−0.16 (−0.42, 0.11)	0	>0.05
Effect of vitamin D supplementation on eGFR	Wang et al. (2019)[30]	4 (290)	WMD	2.13 (−2.06, 6.32)	0	0.32
Effect of vitamin D supplementation on HbA1c	Zhao et al. (2014)[29]	9 (519)	SMD	0.01 (−0.07, 0.09)	0	0.88
	Wang et al. (2019)[30]	10 (629)	WMD	0.02 (−0.09, 0.11)	0	0.84
	Xuan et al. (2023)[41]	3 (161)	WMD	0.02 (−0.37, 0.41)	0	0.92
	Zhang et al. (2017)[42]	9 (617)	WMD	−0.017 (−0.49, 0.15)	0	>0.05
Effect of vitamin D supplementation on FBG	Wang et al. (2019)[30]	3 (230)	WMD	−0.05 (−0.29, 0.20)	0	0.70
Effect of vitamin D supplementation on serum calcium	Gupta et al. (2019)[32]	2 (82)	WMD	0.08 (−0.04, 0.19)	30	0.19
	Zhang et al. (2017)[42]	11 (639)	WMD	0.04 (0.01, 0.06)	35.60	0.1052
Effect of vitamin D supplementation on serum vitamin D	Gupta et al. (2019)[32]	3 (186)	WMD	0.61 (0.04, 1.18)	68	0.04
	Xuan et al. (2023)[41]	6 (350)	WMD	38.24 (32.69, 43.79)	42	<0.00001

CI, confidence interval; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; OR, odds ratio; SMD, standardized mean difference; UACR, urine albumin creatinine ratio; UAER, urine albumin excretion ratio; WMD, weighted mean difference.

Discussion

In this overview of meta-analyses, we tried to provide a broader picture of the existing evidence on the function of vitamin D in the development and progression of DKD. A total of eight meta-analyses were included, examining the association of vitamin D deficiency with the development of DKD and the effect of vitamin D supplementation on the progression of DKD.

Among the various outcomes analysed in this overview, vitamin D deficiency demonstrated a positive association with DKD. Similar findings were reported by Tabatabaei-Malazy et al. who also assessed the therapeutic benefits of vitamin D on various diabetic complications.[43]

The beneficial effects of vitamin D supplementation in diabetes and its complications are not clearly established in the current guidelines on the management of diabetes.[44–48] While some evidence reports a higher incidence of albuminuria in vitamin D deficiency, there is a dearth in clinical trials determining the effectiveness of vitamin D supplementation in managing albuminuria. Therefore, guidelines on the management of CKD and DKD do not recommend routine vitamin D supplementation unless vitamin D deficiency is detected.[49–54] However, our overview found possible evidence suggesting that vitamin D supplementation could possibly reduce 24-h urine protein and UACR. Nevertheless, there was inconclusive evidence for other parameters of renal function, such as UAER, SCr and eGFR. In contrast to our findings, de Oliveira e Silva Ullmann et al.[5] reported that vitamin D supplements could be beneficial in reducing proteinuria and creatinine levels in DKD patients. This variation may be attributed to the difference in the number of primary studies analysed. Our study extracted data from the meta-analyses encompassing 47 primary studies, whereas de Oliveira e Silva Ullmann et al.[5] conducted a systematic based on only 6 primary studies.

The lack of quality evidence for certain outcomes warrants further discussion. One of the major issues is the presence of substantial heterogeneity. This heterogeneity mainly arises from variations in the dose and type of vitamin D supplement used. There is ongoing debate regarding the appropriate form and dosage of vitamin D supplements in the general public and in the patient population, as per different guidelines. The reference daily index of cholecalciferol in the general population varies from 400 to 2000 IU, depending on the guidelines.[35,55–60] Moreover, there are no standard guidelines for vitamin D supplementation in diabetes or CKD.[49] Thus, the optimal dosing regimen for patients with DM or CKD is not defined. Additionally, the type of vitamin D analogue to be used also remains questionable. While cholecalciferol appears to offer some advantage over ergocalciferol in the general population,[61] there is no definitive evidence that cholecalciferol would be superior to ergocalciferol in CKD.[49] Activated forms of vitamin D, such as calcitriol, alfacalcidol or paricalcitol, could be considered for patients with kidney diseases, even so the evidence supporting their use in CKD is weak.[49,58]

The dosing regimens followed in the primary studies included in this overview varied from 5000 to 60,000 IU per week, with a variation in duration from 4 to 48 weeks. Also, the vitamin D analogues used in the study varied from cholecalciferol to ergocalciferol to activated vitamin D forms. This substantial heterogeneity in the dosing regimen and the type of analogue used could be a major reason that the significant positive association observed in observational studies is not being translated into the results of RCTs on the effectiveness of vitamin D supplementation. Moreover, DKD is a progressive and chronic condition, making 'recovery' a less applicable concept compared to acute kidney injury. Management strategies for CKD mainly focus on slowing the progression. Clinical trials on the efficacy of therapeutic options in slowing DKD progression typically span a median duration of at least 2 years to capture meaningful outcomes.[62–64] In contrast, the RCTs included in our study had follow-up durations ranging from 8 to 24 weeks. This relatively short timeframe may limit the ability to fully capture the long-term effects of vitamin D supplementation in reducing the progression.

A lesser number of included studies and a smaller number of participants for meta-analysis could be another potential source of heterogeneity. Less than three studies and/or a total sample size of less than 200 were included in the pooled results for the effectiveness of vitamin D supplementation on UAER,[32] SCr,[32,41] HbA1c,[41] serum calcium[32] and serum vitamin D.[41] Evidence suggests that underpowered studies have become a major source of bias in meta-analyses, with smaller sample sizes resulting in a noticeable bias, particularly

when estimated for SMD and OR in meta-analyses.[65,66] This could be a possible explanation for the lack of significance for the impact of vitamin D supplementation on kidney function and other related parameters. Therefore, to accurately assess the benefits of vitamin D on kidney function, further studies with adequate power and larger sample sizes are required.

RCTs on the effects of vitamin D supplementation on kidney function in DKD patients mostly compare the investigation group with either standard treatment of DKD or active control with ARBs, or with placebo. Evidence suggests that there could be systematic differences in response rate results from active-controlled trials when compared with placebo-controlled trials.[67,68] The subgroup analysis in the meta-analyses included in this overview showed a significant improvement in kidney function following vitamin D supplementation in active-controlled trials as compared to placebo-controlled trials.[42] These findings were consistent with the systematic reviews on the pleiotropic effects of vitamin D supplements on DKD.[69,70] Nevertheless, vitamin D may be regarded as a cost-effective adjuvant along with standard DKD management, considering a wider safety margin. However, large-scale trials are needed in the future to evaluate this further.

Our overview of meta-analyses has several strengths. It offers a systematic, comprehensive overview of the evidence on the role of vitamin D in the development and progression of DKD from the existing meta-analyses. The quality and certainty of evidence were evaluated using validated tools such as AMSTAR-2. We also detected gaps in the evidence that indicate a need for future research.

This study also has some limitations. Only studies included in a meta-analysis of interest are included in the study. Therefore, there is a chance to miss out on some of the relevant research, especially those that are recently published. Also, most of the primary studies from the meta-analysis of RCTs were in Chinese and, hence, not retrievable. Thus, the pooling of data was not possible in the case of the effectiveness of vitamin D supplementation on various outcomes, and the evidence was derived based on the analysis results of the meta-analyses.

Another major limitation is that a smaller number of included studies and, consequently, a smaller number of study participants in pooled analysis has greatly affected the certainty of evidence. Moreover, there was a wide variation in the study characteristics, such as the vitamin D dosing, duration and analogue used, all of which could potentially influence the quality of the evidence. The average duration of studies is considerably shorter than the clinical trial assessing the role of various therapeutic options in CKD. Risk of bias, AMSTAR-2-based methodological quality and significant inconsistencies present in the study results could be additional factors that could have affected the quality of the evidence.

Future low-bias RCTs with larger sample sizes are necessary to enhance the quality and confirm the clinical applicability of evidence. These studies should focus on comparing different analogues of vitamin D supplementation to identify the optimal dosing regimen, including the appropriate dose, frequency and duration of vitamin D supplementation, with respect to the stage of DKD. Additionally, studies exploring the underlying mechanistic pathways for the action of vitamin D in DKD, would provide deeper insights and strengthen the clinical evidence.

Conclusion

The current overview indicates that vitamin D deficiency is significantly correlated with the development of DKD. Furthermore, a reduction in proteinuria appears to be the most consistent outcome associated with vitamin D supplementation. However, this alone may be insufficient to influence clinical practice or inform guidelines, given the lack of consistent evidence regarding its impact on other renal function markers, such as SCr and eGFR.

Vitamin D may serve as an adjunctive therapy alongside standard treatment for DKD, particularly in reducing proteinuria. However, long-term, high-quality follow-up studies with a consistent methodology, larger sample sizes and the assessment of additional renal parameters are required to determine the optimal dosing regimen and clarify its impact on the progression of DKD.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
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Data is available within the article. The authors confirm that the data supporting the findings of this study are available within the article.

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