Review Article:

Vitamin D Deficiency and Risk of Diabetic Microvascular Complications: A Systematic Review

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Abstract:

Vitamin D deficiency is highly prevalent among individuals with diabetes mellitus and may contribute to the development and progression of microvascular complications, including nephropathy, neuropathy, and retinopathy. This systematic review assessed the relationship between vitamin D status and these complications. A comprehensive search of PubMed, European PMC, Google Scholar, CORE, and DOAJ was conducted for studies published between January 2015 and March 2025, focusing on original research evaluating vitamin D levels and diabetic microvascular outcomes in adults with type 1 or type 2 diabetes. Forty-nine studies met the inclusion criteria, and due to substantial methodological heterogeneity, a narrative synthesis was performed. The majority of included studies demonstrated a significant association between low serum vitamin D levels and increased severity of diabetic complications. For nephropathy, vitamin D supplementation was commonly linked to reduced albuminuria, improved glomerular filtration rate, and modulation of the renin–angiotensin–aldosterone system. In diabetic neuropathy, vitamin D repletion was associated with improvements in pain scores, nerve conduction parameters, and inflammatory cytokine profiles. Although evidence for diabetic retinopathy was comparatively limited, several clinical and observational studies reported that sufficient vitamin D levels may enhance responsiveness to anti-VEGF therapy, improve visual outcomes, and reduce retinal edema. Overall, the findings suggest that vitamin D may play a protective role in mitigating the burden of diabetic microvascular complications. However, variations in study design, dosing strategies, and outcome measures highlight the need for well-designed, large-scale randomized controlled trials to clarify causality and determine optimal supplementation protocols for diabetic populations.

Keywords:

Vitamin D, Diabetes Mellitus, Retinopathy, Neuropathy, Nephropathy, Microvascular Complications

Introduction:

Diabetes mellitus (DM) is a long-standing metabolic disorder defined by elevated blood glucose levels due to impaired insulin secretion, insulin resistance, or both. It continues to pose a significant public health burden, with over 828 million adults affected worldwide. India and China represent the largest shares of the global diabetic population, followed by countries such as the United States, Pakistan, Indonesia, and Brazil[1-3]. The disease contributes to numerous chronic complications, particularly microvascular outcomes that include diabetic nephropathy, neuropathy, and retinopathy, all of which can result in long-term disability and reduced quality of life[4].

Diabetic retinopathy (DR) remains the most common cause of non-traumatic vision loss among working-age adults. In 2010, an estimated 93 million individuals globally were diagnosed with DR, and approximately 28 million had advanced or vision-threatening forms of the condition[4,5]. Meanwhile, diabetic nephropathy is a primary contributor to chronic kidney disease and end-stage renal failure, and diabetic neuropathy can lead to significant pain, sensory impairment, and ulceration. These complications not only increase patient morbidity but also place a heavy burden on healthcare systems[6].

Vitamin D, a fat-soluble vitamin primarily synthesized in the skin upon exposure to ultraviolet light and obtained in smaller amounts through diet, is well known for its regulatory role in calcium and phosphate metabolism. However, recent research highlights its involvement in broader physiological processes, such as immune regulation, modulation of inflammatory responses, insulin sensitivity, and maintenance of vascular function[6–8]. The metabolic activation of vitamin D involves hepatic hydroxylation to 25-hydroxyvitamin D [25(OH)D], followed by conversion to its active form in the renal tubules. Impaired kidney function frequently seen in individuals with diabetes may hinder this conversion, leading to reduced levels of circulating vitamin D[6–8]. Several studies have indicated that vitamin D may exert protective effects against microvascular damage due to its anti-inflammatory, anti-fibrotic, and endothelium-stabilizing properties[9–11]. These mechanisms are particularly relevant in the pathogenesis of diabetic microvascular complications. Despite this, evidence from clinical studies remains varied, and the impact of vitamin D supplementation on the progression

or prevention of these complications is still under investigation[11,12]. Given the high prevalence of vitamin D deficiency among patients with diabetes and the increasing interest in its potential role in mitigating microvascular complications, it is important to assess the available evidence systematically. This review aims to evaluate the relationship between vitamin D deficiency and diabetic complications, particularly retinopathy, neuropathy, and nephropathy, by synthesizing data from studies published over the past decade.

Problem Statement:

Diabetes mellitus leads to serious microvascular complications, including retinopathy, neuropathy, and nephropathy, which contribute significantly to patient morbidity. Concurrently, vitamin D deficiency is highly prevalent among diabetic individuals and may influence the pathogenesis of these complications through its roles in inflammation, vascular function, and glucose metabolism. Although several studies have explored this association, their findings remain inconsistent, limiting clinical application. A systematic evaluation of the evidence is needed to clarify the potential link between vitamin D deficiency and diabetic complications.

Rationale:

Vitamin D has been shown to exert a range of biological effects beyond its classical role in bone metabolism, including modulation of inflammatory pathways, enhancement of vascular endothelial function, and regulation of insulin sensitivity and secretion [(6–8)]. These mechanisms are directly relevant to the development and progression of diabetic microvascular complications such as retinopathy, neuropathy, and nephropathy. Given the high prevalence of vitamin D deficiency among individuals with diabetes mellitus and its potential role in vascular protection and metabolic regulation, understanding this association has significant clinical relevance[9–11]. Although multiple studies have explored the link between vitamin D deficiency and diabetic complications, their findings remain inconsistent due to variability in study populations, methodologies, and outcome measures[11,12]. A systematic review is therefore essential to synthesize current evidence, identify gaps, and support evidence-based strategies for risk assessment and management in diabetic care, as summarized in Table 1.

Table 1: PICOT Framework for the Systematic Review.
Outlines the population (P), intervention (I), comparator (C), outcome (O), and time frame (T) that guided the systematic review's inclusion criteria.

P	Adults with diabetes mellitus
I	Vitamin D supplementation
C	No supplementation or normal vitamin D levels
O	Incidence/severity of diabetic complications
T	2015–2025 (publication range)

Research question:

What is the association between vitamin D deficiency and the development or severity of diabetic microvascular complications specifically retinopathy, neuropathy, and nephropathy in patients with diabetes mellitus?

Objectives:

This review aimed to systematically evaluate the existing literature on the association between vitamin D deficiency and the risk, severity, or progression of diabetic microvascular complications, including retinopathy, neuropathy, and nephropathy.

Method:

Search Strategy:

A structured literature search was carried out using five databases: PubMed, European PMC, Google Scholar, CORE, and Directory of Open Access Journals (DOAJ), in order to identify relevant studies published between January 2015 and March 2025. The search employed combinations of the following terms: "Vitamin D," "Deficiency," "Diabetes," "Retinopathy," "Neuropathy," and "Nephropathy," linked using Boolean operators "AND" and "OR." Only studies published in English and with freely accessible full texts were considered. The reference lists of selected articles were also reviewed to capture any additional studies meeting the inclusion criteria.

Study Selection and Screening:

All identified citations were imported into Rayyan, an online tool for systematic review screening. Duplicate records were removed using Zotero, and two reviewers independently screened titles and abstracts. Full-text review was conducted for studies

that appeared relevant. Any disagreements during the selection process were resolved by consensus or third-party arbitration.

Inclusion and Exclusion Criteria:

Studies were included if they met the following criteria:

- Investigated individuals with a confirmed diagnosis of type 1 or type 2 diabetes mellitus.
- Examined the relationship between vitamin D levels and diabetic microvascular complications such as retinopathy,neuropathy,ornephropathy.
- Employed original research designs, including observational (cross-sectional, case-control, or cohort) or interventional studies.
- Were published within the specified date range and in the English language.

The following were excluded:

- Review articles, meta-analyses, editorials, and case reports.
- Studies lacking full-text availability or not published in English.
- Research not directly focused on the association between vitamin D deficiency and diabetic complications.

Data Extraction and Management:

A predefined data extraction sheet was used to systematically collect relevant information from each study. Extracted data included:

- Author(s), year, and country of publication.
- Study design, sample size, population characteristics.
- Type of diabetic complication studied and method of assessment.
- Measurement and categorization of vitamin D status.
- Major findings related to the association between vitamin D and diabetic complications.

Assessment of Confidence in Review Findings:

The final articles included in this review were assessed for quality using different tools. Each study was assigned an appropriate quality appraisal tool based on assumed study design types, and a summary is provided for each, which provided a structured evaluation across key domains such as study design, sampling, data analysis, ethical considerations, and clarity of reporting.

Studies with strong methodological quality, adequate sample sizes, and clearly defined outcomes were given greater weight in the synthesis. Confidence in the evidence was categorized as follows:

- **High Confidence:** Findings supported by multiple high-quality studies with

consistent results and well-defined methodology. These studies offered clear associations between vitamin D status and diabetic complications.

- **Moderate Confidence:** Results supported by several studies with minor methodological limitations, such as small sample sizes or incomplete control for confounders. These findings suggest a probable association, though further evidence is needed for confirmation.
- **Low Confidence:** Evidence based on studies with notable methodological weaknesses, including inconsistent reporting, unclear outcome definitions, or limited generalizability. These findings should be interpreted cautiously.

Overall, the body of evidence suggests a potential link between vitamin D deficiency and the severity or progression of diabetic microvascular complications. However, due to variations in study design, populations, and outcome measures, the level of confidence across findings ranged from moderate to high. Future research with standardized definitions, dosing protocols, and longitudinal designs is needed to strengthen the evidence base and confirm causality.

Data Synthesis:

Due to variability in study methodologies, populations, and outcomes, statistical pooling was not feasible. Therefore, a narrative synthesis approach was adopted. Findings were organized by complication type retinopathy, neuropathy, and nephropathy and summarized according to study design, effect direction, and strength of association.

Quality Appraisal of Included Studies:

The methodological rigor of the included studies was appraised using the tool developed by Hawker et al.[13]. This tool evaluates nine components, including study design, sampling, data analysis, ethical considerations, and presentation of findings. Each element was rated on a scale from 1 (very poor) to 4 (good), providing a comprehensive quality profile for each study, and the results of this assessment are summarized in Table 2.

Table 2: showing the quality assessment of the included studies.

Summarizes the quality ratings of all 49 included studies using different tools. Each study was assigned an appropriate quality appraisal tool based on assumed study design types, and a summary is provided for each.

	Study	Tool Used	Quality assessment
1	[Nugroho et al., 2025][14]	ROBINS-I	High
2	[Dervis et al., 2025][15]	NIH Quality Assessment tool	Serious

3	[Melake et al., 2025][16]	NIH Quality Assessment tool	Serious
4	[Hung et al., 2025] [17]	NIH Quality Assessment tool	Low
5	[Melake et al., 2025][18]	NIH Quality Assessment tool	High
6	[Yeung WG et al., 2024][19]	ROBINS-I	Serious
7	[Nataraj et al., 2024][20]	NIH Quality Assessment tool	Moderate
8	[Kang et al., 2024][21]	SYRCLE	Low
9	[Obaid et al., 2024][22]	NIH Quality Assessment tool	High
10	[Askari et al., 2024][23]	RoB 2	Low
11	[Sun et al., 2024][24]	NIH Quality Assessment tool	Serious
12	[Xu et al., 2024][25]	ROBINS-I	Serious
13	[Riaz et al., 2023][26]	SYRCLE	Serious
14	[Gnudi L et al., 2023][27]	AXIS	Serious
15	[Stathi D et al., 2023][28]	AXIS	Low
16	[He et al., 2023][29]	AXIS	High
17	[Chen et al., 2023][30]	NIH Quality Assessment tool	Low
18	[Marton & Szabo, 2023][31]	ROBINS-I	Moderate
19	[Karalliedde J et al., 2023][32]	RoB 2	High
20	[Fekri S et al., 2022][33]	NIH Quality Assessment tool	Moderate
21	[Lu Y et al., 2022][34]	RoB 2	Low
22	[Liu et al., 2022][35]	ROBINS-I	Serious
23	[Kamalanathan et al., 2022][36]	NIH Quality Assessment tool	Low
24	[Aref et al., 2022][37]	NIH Quality Assessment tool	Low
25	[Rasouli N et al., 2022][38]	AXIS	Serious
26	[Girard et al., 2021][39]	ROBINS-I	Moderate
27	[Janker et al., 2021][40]	ROBINS-I	Moderate
28	[Liyanage et al., 2021][41]	SYRCLE	Moderate
29	[Karonova T et al., 2020][42]	NIH Quality Assessment tool	Serious
30	[Silva et al., 2020][43]	NIH Quality Assessment tool	Low
31	[Kelly et al., 2020][44]	RoB 2	Low
32	[Xiao et al., 2020][45]	AXIS	Serious
33	[Butler et al., 2020][46]	ROBINS-I	Moderate

34	[de Jong MA et al., 2019][47]	RoB 2	Serious
35	[Jovanovich A et al., 2019][48]	NIH Quality Assessment tool	Moderate
36	[Boer et al., 2019][49]	NIH Quality Assessment tool	Moderate
37	[Liyanage P et al., 2018][50]	NIH Quality Assessment tool	Serious
38	[Levin A et al., 2017][51]	SYRCLE	Serious
39	[Keyzer et al., 2017][52]	AXIS	Serious
40	[Alam U et al., 2017][53]	ROBINS-I	High
41	[Jiang & Zhang, 2017][54]	NIH Quality Assessment tool	Serious
42	[Liyanage et al., 2017][55]	SYRCLE	Low
43	[Chous AP et al., 2016][56]	RoB 2	High
44	[Saeedi et al., 2016][57]	NIH Quality Assessment tool	High
45	[Momeni et al., 2016][58]	NIH Quality Assessment tool	High
46	[Tiryaki Ö et al., 2016][59]	RoB 2	Moderate
47	[Thethi TK et al., 2015][60]	NIH Quality Assessment tool	Moderate
48	[Joergensen et al., 2015][61]	ROBINS-I	Low
49	[Shehab D et al., 2015][62]	RoB 2	Moderate

Results:

Initially, a total of 35,006 records were identified from all the databases (PubMed 4,300; European PMC 20,751; Google Scholar 9,520; CORE 435; DOAJ 0), and 5,264 duplicates were found. After removal of duplications, 29,742 records remained. These records were initially screened (at the title and abstract level). Most of them were excluded as non-relevant to inclusion criteria. Subsequently, 528 full-text articles and trial records were assessed for eligibility. Common reasons for exclusion included: studies not involving diabetic populations; studies not assessing the association between vitamin D status and diabetic microvascular complications; review articles or meta-analyses; case reports; non-English language publications; and those lacking full-text accessibility. Finally, 49 studies were subjected to final synthesis. The entire study selection process is illustrated in the PRISMA flow diagram (Figure 1). Illustrates the process of literature identification, screening, eligibility, and inclusion according to PRISMA 2020 guidelines. It summarizes the selection of 49 studies from 35,006 records retrieved from five databases.

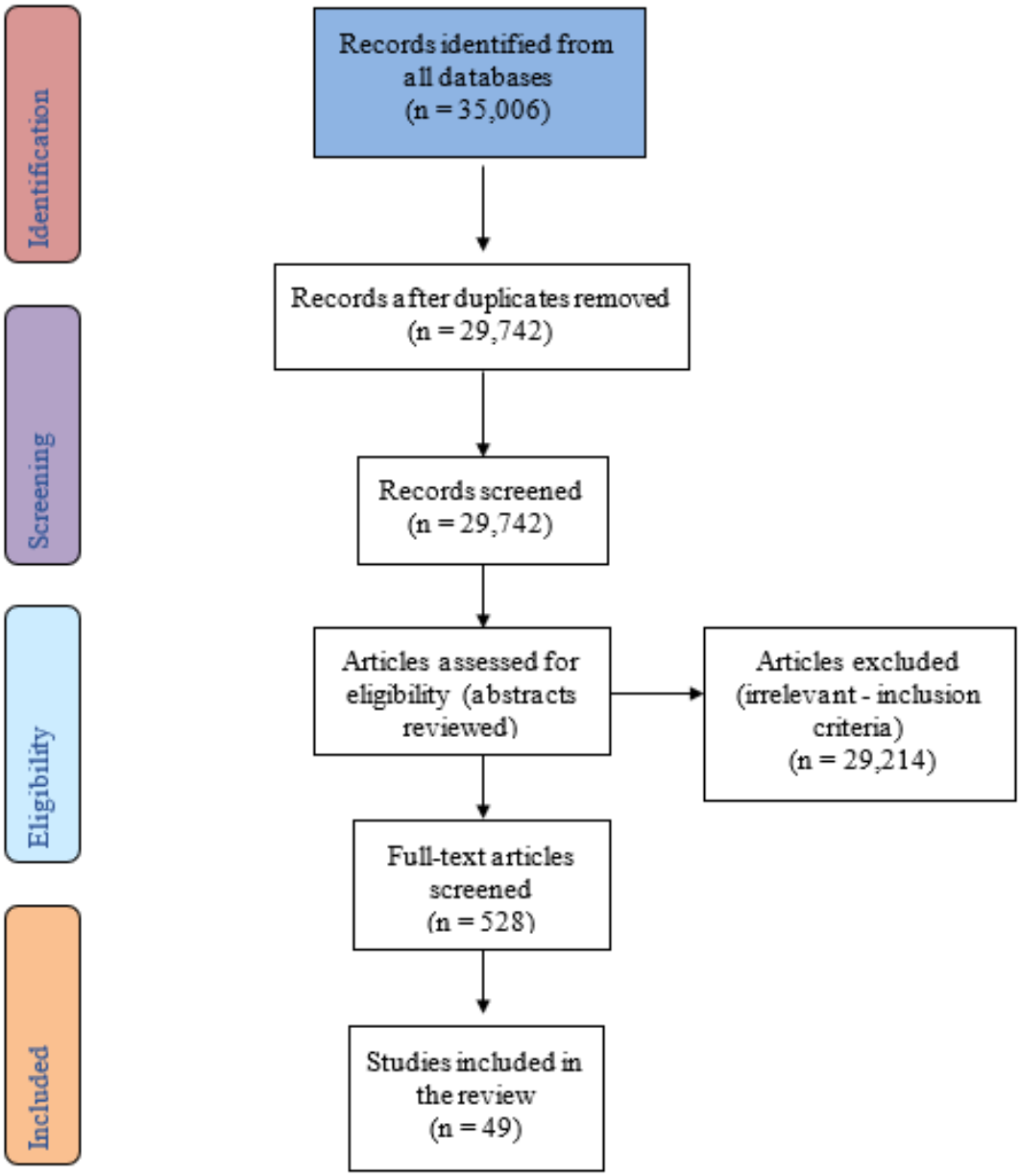


Figure 1: PRISMA shows Flow Diagram Summarizing the Selection of Eligible Studies .

These included 17 studies from PubMed, 16 studies from European PMC, 16 studies from Google Scholar, and none from CORE and DOAJ. Regarding study design, 13 were randomized controlled trials (RCTs), 13 were cross-sectional studies, 10 were prospective cohort studies, 7 were retrospective cohort studies, 6 were case–control studies, and one was a Mendelian randomization study.

These 49 studies explored the relationship between vitamin D deficiency and three key diabetic microvascular complications: nephropathy (21 studies), neuropathy (17

studies), and retinopathy (11 studies).

Nephropathy:

Among the 21 studies focusing on diabetic nephropathy, the majority reported that vitamin D supplementation particularly in its active forms such as calcitriol and paricalcitol was associated with reduced albuminuria, improved glomerular filtration rate (GFR), and downregulation of the renin–angiotensin–aldosterone system (RAAS), and lowered inflammatory markers (IL-6, TNF-**α**). For instance, Liyanage et al.[55] observed a significant reduction in urinary albumin-to-creatinine ratio and an increase in eGFR following vitamin D therapy. Similarly, Tiryaki et al.[59] noted a decline in urinary angiotensinogen levels, suggesting a potential nephroprotective mechanism mediated via RAAS suppression. These effects were more prominent in early stages of chronic kidney disease (CKD) and in type 2 diabetic populations.

Neuropathy:

A total of 17 studies evaluated the role of vitamin D in diabetic neuropathy. High-dose cholecalciferol or active vitamin D analogs were frequently associated with improvement in neuropathic symptoms, reduced pain scores, enhanced nerve conduction, and modulation of neuroinflammatory cytokines. For example, Karonova et al.[42] reported improvements in neuropathy symptom scores (NSS), reductions in inflammatory markers (e.g., IL-6), and increased anti-inflammatory cytokines (e.g., IL-10) following 40,000 IU/week of cholecalciferol. Alam et al.[53] demonstrated a significant enhancement in the emotional well-being domain of the NeuroQoL scale post-supplementation, underscoring improvements in patient-reported outcomes.

Retinopathy:

The 11 studies addressing diabetic retinopathy revealed promising findings, as it was demonstrated that vitamin D has the potential to improve response to anti-VEGF therapy, enhance visual acuity and reduce macular thickness, as well as modulate microvascular inflammation in the retina. For example, Fekri et al.[33] found that correcting hypovitaminosis D in patients receiving intravitreal bevacizumab for diabetic macular edema led to enhanced visual outcomes and greater reductions in central macular thickness. Other observational studies revealed lower risk of retinopathy severity in patients with higher serum 25(OH)D levels.

Mechanistic and Metabolic Effects:

Across all categories of complications, several studies reported anti-inflammatory, anti-fibrotic, and endothelial-stabilizing effects of vitamin D. Additionally, vitamin D was frequently linked to improved

markers of metabolic control, including insulin resistance (HOMA-IR), **β**-cell function (HOMA-**β**), and reduced systemic inflammatory markers (e.g., hsCRP, TNF-**α**). These systemic effects support the biological plausibility of vitamin D's role in modifying the trajectory of diabetic complications.

Summary of Outcomes:

An overview of outcome distribution by complication is presented in Table 3. A high proportion of studies reported positive clinical associations:

- 85.7% (18 out of 21) of nephropathy studies demonstrated improved renal outcomes following vitamin D supplementation.
- 82.3% (14 out of 17) of neuropathy studies reported significant improvements in symptom scores, inflammation, or nerve conduction.
- 63.6% (7 out of 11) of retinopathy studies observed improved visual response or prevention of disease progression associated with sufficient vitamin D levels.

Table 3 summarizes the pooled findings from 49 studies examining the relationship between vitamin D deficiency and diabetic complications (retinopathy, neuropathy, nephropathy).

Table 3: Summary of Study Outcomes by Complication Type.
Provides an overview of the number of studies addressing each complication (nephropathy, neuropathy, retinopathy), the percentage showing improved outcomes, and the commonly reported clinical improvements.

Complication	Number of Studies	Improved Outcomes (%)	Common Improvements
Nephropathy	21	85.7%	↓ Albuminuria, ↑ GFR, RAAS modulation
Neuropathy	17	82.3%	↓ Pain, ↑ Nerve conduction, ↓ Inflammation
Retinopathy	11	63.6%	↓ Retinal edema, ↑ Visual response, ↓ VEGF

Discussion:

This systematic review evaluated the relationship between vitamin D deficiency and diabetic microvascular complications, synthesizing findings from 49 studies that examined nephropathy, neuropathy, and retinopathy. Overall, the evidence demonstrates a consistent association between low serum 25(OH)D levels and greater burden or severity of these complications. Although this trend is evident across study designs, the strength of the association varies by complication type, and important methodological limitations should be considered.

Nephropathy:

Among the included complications, diabetic nephropathy (DN) had the strongest and most consistent evidence linking low vitamin D levels with adverse renal outcomes. Multiple clinical trials demonstrated improvements in albuminuria, glomerular filtration, and RAAS activity following supplementation with active vitamin D analogs. These findings suggest a mechanistically plausible renoprotective effect, likely mediated by modulation of inflammatory and hormonal pathways. Observational analyses by Zhao et al.[3] , Hassan et al.[63], and Vishnumoorthy & Bhat[65] reinforce this association, demonstrating that vitamin D deficiency is significantly more prevalent among individuals with DN. However, heterogeneity in dosing regimens, renal outcome definitions, and follow-up durations limits the ability to determine optimal supplementation strategies.

Neuropathy:

The evidence for diabetic peripheral neuropathy (DPN) also supports a meaningful link between vitamin D deficiency and neuropathic impairment. Studies consistently reported improvements in nerve conduction, pain scores, and inflammatory profiles following vitamin D repletion. The strong gradient of vitamin D deficiency among DPN populations, as observed by Zhao et al.[3], Hassan et al.[63], and Vishnumoorthy & Bhat[64], further underscores its potential clinical relevance. Nevertheless, many neuropathy trials had small sample sizes or lacked standardized electrophysiological testing, which restricts the generalizability of the findings. The possibility that vitamin D deficiency reflects broader metabolic dysregulation rather than a causal contributor to neuropathy cannot be excluded.

Retinopathy:

Although fewer studies assessed diabetic retinopathy (DR), emerging evidence indicates that lower vitamin D levels may contribute to increased disease severity and poorer treatment response. Interventional studies, such as those by Fekri et al.[33], demonstrated that correcting vitamin D deficiency may enhance visual recovery and reduce macular edema, particularly when combined with anti-VEGF therapy. These findings are consistent with the large meta-analysis by Petrea et al.[65], which demonstrated significantly lower mean 25(OH)D levels among DR patients and a clear dose–response relationship with retinopathy risk. The substantial heterogeneity reported in their analysis (I^2 = 89%) highlights important inconsistencies across existing research, including variations in DR grading systems, vitamin D thresholds, and patient populations.

Biological Plausibility and Broader Metabolic Implications:

The observed associations are supported by well-established biological mechanisms. Vitamin D can modulate inflammation, oxidative stress, endothelial dysfunction, and fibrotic pathways all fundamental to the pathogenesis of microvascular disease. Improvements in systemic metabolic markers such as HOMA-IR, HbA1c, hsCRP, IL-6, TNF-α, and lipid parameters further reinforce this mechanistic rationale. These systemic findings align with the broader conclusions of Isa et al.[66] , who emphasized the role of vitamin D deficiency in worsening both microvascular and macrovascular outcomes among diabetic patients.

Comparison With Previous Systematic Reviews:

The conclusions of this review are consistent with prior systematic evidence. Petrea et al.[66] demonstrated a significant association between low vitamin D levels and increased risk of diabetic retinopathy, supporting the trends observed here. Similarly, Isa et al.[66] reported strong links between vitamin D deficiency and multiple diabetic complications, particularly nephropathy and neuropathy, reinforcing the biological plausibility of the associations highlighted in this review. These previous syntheses converge with the present findings, underscoring the potential importance of vitamin D status in diabetic microvascular health.

Limitations:

This review has several important limitations. The restriction to English-language publications may have introduced language bias and excluded relevant international evidence. The use of multiple heterogeneous databases particularly Google Scholar, which includes non–peer-reviewed sources may have increased variability in search precision. Substantial differences across studies in vitamin D thresholds, dosing regimens, diagnostic criteria, and follow-up durations resulted in high heterogeneity and prevented quantitative pooling. Many observational studies were subject to confounding, while several interventional trials lacked standardized protocols or long-term assessment. These methodological variations limit causal interpretation and highlight the need for large, well-designed randomized controlled trials.

Conclusion:

This systematic review demonstrates a consistent association between vitamin D deficiency and the major diabetic microvascular complications—nephropathy, neuropathy, and retinopathy. Across the included studies, adequate vitamin D status was frequently linked with improvements in

renal markers, neuropathic symptoms, and retinal outcomes, supported by plausible anti-inflammatory and endothelial-protective mechanisms.

Despite these encouraging findings, interpretation is limited by substantial heterogeneity in study populations, supplementation regimens, diagnostic criteria, and outcome measures. These methodological variations prevent firm conclusions regarding causality and optimal therapeutic dosing. Future research is needed, particularly well-designed, adequately powered randomized controlled trials with standardized vitamin D protocols, to clarify the clinical role of supplementation and inform evidence-based guidelines for diabetic care.

Strengths and limitations of the study:

This review's strengths include a focused research question, a comprehensive search of five databases, and the use of a validated quality appraisal tool. Including both observational and interventional studies provided a broad overview of clinical evidence.

The main limitations relate to methodological differences among studies and the absence of a meta-analysis due to heterogeneity. Despite these limitations, the review offers valuable insights into the potential role of vitamin D in diabetic microvascular complications and identifies key areas for future research.

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The authors performed all writing, editing, analysis, and interpretation manually. No automated tools were used for data extraction, data interpretation, or manuscript drafting. Standard language-editing software was used only for minor grammar and formatting refinement.

Conflict of Interest:

The author declares no conflict of interest.

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