The Role of Vitamin D and Its Receptor Signaling in Diabetic Nephropathy and the Current Status of Research: A Literature Review

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ABSTRACT

Diabetic kidney disease (DKD) is one of the common and serious complications of diabetes mellitus, with a complex pathogenesis and a lack of ideal treatment options in clinical practice. In recent years, the protective role of vitamin D and its receptor signaling pathway in DKD has garnered widespread attention. Vitamin D plays an important role in the onset and progression of DKD by participating in the regulation of insulin secretion, inhibiting inflammatory responses, attenuating podocyte injury, modulating the renin-angiotensin system (RAS), and inhibiting renal interstitial fibrosis through its receptor (VDR). Studies on the use of vitamin D and its receptors in DKD have increased gradually in recent years, with a focus on the development of vitamin D analogs and the clinical application of VDR activators. This study reviewed the mechanisms of vitamin D and its receptor in diabetic nephropathy, as well as the potential for therapeutic applications and associated adverse effects. It also analyzed current research hotspots and development trends based on bibliometrics. Future research should focus on further optimizing vitamin D-based therapeutic strategies to achieve better clinical efficacy and safety.

Keywords: *Diabetic nephropathy, vitamin D, vitamin D receptor, kidney injury, bibliometrics.*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease that has become a major public health issue worldwide due to its rising prevalence.[1] Diabetes can lead to multiple organ dysfunctions, often associated with damage caused by chronically high blood glucose levels.[2] Diabetic Kidney Disease (DKD) is a common complication, affecting about 40% of diabetic patients.[3] Chronic hyperglycemia damages the renal microvasculature, leading to renal hypertrophy and glomerular basement membrane thickening, which further induces glomerulosclerosis and tubulointerstitial fibrosis.[4] The clinical manifestations of diabetic nephropathy include a progressive decline in renal function with persistent albuminuria. Diabetic kidney disease (DKD), chronic kidney disease (CKD), and end-stage renal disease (ESRD) represent different stages of kidney disease progression, with ESRD being the leading cause of death in diabetic patients.[5] Effectively controlling disease progression and reversing kidney damage is a major research focus in DKD treatment. Currently, the main interventional treatments for DKD include nutritional management, glucose-lowering drugs, blood pressure control, and inhibition of the renin-angiotensin system. However, existing treatment protocols have not achieved satisfactory results.[6,7]

Vitamin D is a sterol-derived, multifunctional fat-soluble micronutrient with important physiological functions in the body.[8] The body's

vitamin D requirement comes from two main sources: endogenous synthesis in the skin through sunlight exposure and dietary intake from food or supplements.[9] Approximately 80% of vitamin D is produced endogenously as vitamin D_3 through UV irradiation of the skin, while the remaining 20% is obtained through dietary intake of vitamin D_2 and vitamin D_3, which are primarily found in dairy products, breads, grains, oily fish, and other foods.[10] Vitamin D helps maintain normal blood calcium and phosphorus levels by promoting intestinal absorption of these minerals, which are essential for bone development and maintenance of bone density.[8] Mechanistically, vitamin D enhances calcium absorption in the small intestine by up-regulating the expression of calcium transport proteins, the epithelial calcium channel TRPV6, and the calcium-binding protein 9K.[11] Additionally, vitamin D is involved in various physiological functions, including cancer prevention and treatment, immune response regulation, and modulation of endocrine functions. Numerous studies have shown that the enzyme 1-α-hydroxylase is present in various tissue cells and immune cells and is capable of generating the active form of vitamin D, $1,25(OH)_2D_3$. This active form exerts its biological effects by binding to the vitamin D receptor (VDR) in target tissues.[12,13] Vitamin D not only plays an important role in maintaining skeletal homeostasis but also has a wide range of regulatory functions in various physiological and pathological processes.

The vitamin D receptor (VDR) is a member of the nuclear receptor superfamily (NRs) and is involved in regulating calcium and phosphorus metabolism, bone health, and immune function, primarily through binding to vitamin D.[14] VDR is expressed in more than 30 tissues, including the gut, kidney, cartilage, bone, and lymphocytes.[15] VDR is expressed in more than 30 tissues such as the gut, kidney, cartilage, bone, and lymphocytes.[15] In the kidney, VDR expression is widespread, found in proximal and distal tubular epithelial cells, glomerular podocytes, paraglomerular organelles, mesangial cells, collecting duct cells, and renal capsule cells.[16] Vitamin D deficiency is one of the leading causes of all-cause mortality in patients with chronic kidney disease (CKD), potentially related to mineral metabolism disorders and impaired skeletal integrity due to deficiencies in vitamin D and its receptor signaling. Upon activation, VDR inhibits iron porphyrin deposition in renal tubular epithelial cells by up-regulating the expression of the NFE2-associated factor 2/heme oxygenase 1 (Nrf2/HO-1) signaling pathway, thereby effectively attenuating renal tubular injury.[17] The role of vitamin D and its receptor is crucial for renal protection and the prevention of chronic kidney disease.

Vitamin D and its receptor play a key role in the pathogenesis of diabetic kidney disease (DKD). In recent years, novel therapeutic strategies for DKD, including studies on vitamin D analogs and vitamin D receptors (VDRs), have received significant attention. This paper reviews the role and therapeutic strategies of vitamin D and its receptor signaling pathway in diabetic nephropathy and analyzes the current research hotspots and development trends using bibliometrics.

Renoprotective Effects of Vitamin D and Its Receptor Signaling in Patients with Diabetic Nephropathy

Vitamin D deficiency is an independent risk factor for the development of diabetes. Both animal and clinical studies have shown that vitamin D levels are negatively associated with the risk of diabetic kidney disease (DKD).[18] Vitamin D and its receptors play an important role in protecting kidney function in patients with DKD.[19] Vitamin D and its receptor signaling are involved in a wide range of physiological functions, including the regulation of vascular endothelial function, the renin-angiotensin-aldosterone system, inflammatory responses, and metabolic immunity.[20] In this review, we systematically summarize the mechanisms of vitamin D and its receptor signaling in renal protection for patients with diabetic nephropathy. These mechanisms include insulin secretion, inflammatory response, podocyte injury, renin-angiotensin system regulation, and interstitial fibrosis.

Vitamin D and Its Receptor Signaling are Involved in the Regulation of Insulin Secretion and Sensitivity

Vitamin D deficiency is considered an independent risk factor for the development

of diabetes.[21] Several animal experiments and clinical studies have shown that vitamin D levels are negatively associated with the risk of developing diabetic kidney disease (DKD).[18] Vitamin D deficiency is also linked to insulin deficiency and impaired insulin secretion.[18] Vitamin D deficiency is strongly associated with impaired insulin secretion.[22] Serum vitamin D levels are positively correlated with β-cell function and insulin sensitivity.[23] In rat studies, vitamin D deficiency resulted in impaired insulin secretion from pancreatic β-cells, which was restored by exogenous vitamin D supplementation.[24,25] An intervention study in hemodialysis patients demonstrated that vitamin D can improve glucose utilization by promoting insulin secretion and increasing insulin sensitivity.[26] Supplementation with vitamin D or its active metabolites has been shown not only to enhance insulin secretion but also to improve insulin sensitivity throughout the body, offering potential therapeutic benefits for managing diabetes mellitus.[27]

Vitamin D and Its Receptor Signaling Play a Role in Regulating Inflammation

Inflammatory responses not only exacerbate insulin resistance but also contribute to the development of diabetic nephropathy (DKD).[19] The pathological development of DKD is closely associated with the infiltration of leukocytes, monocytes, and macrophages into the kidney.[28] Several studies have shown that inflammatory factors such as IL-1, IL-6, and IL-18 play important roles in the progression of DKD.[29-31] Mechanistically, IL-1 can upregulate vascular endothelial cell permeability and induce glomerular microcirculatory disturbances.[30,31] I IL-6 stimulates the proliferation of tethered cells, which promotes the expression of fibronectin and enhances epithelial cell permeability.[32,33] IL-18 is associated with increased cell permeability and the development of microvascular complications such as nephropathy.[34] Macrophage polarization plays a key role in the development of DKD, and vitamin D promotes the conversion of M1 to M2-type macrophages.[35,36] M1-type macrophages promote inflammation and tissue damage, while M2-type macrophages have anti-inflammatory and tissue repair properties.[37,38] M2 macrophages can protect renal function by inhibiting podocyte injury and glomerular dysfunction.[35,38] Overall, controlling the inflammatory response, especially through the regulation of macrophage polarization, maybe a crucial strategy in combating DKD.

Vitamin D and Its Receptor Signaling Attenuate Podocyte Damage by Inhibiting Apoptosis and Inducing Autophagy

Podocytes are a crucial component of the glomerular filtration barrier, and vitamin D can mitigate podocyte damage, thus offering protective effects on kidney function.[35,38] Vitamin D and its receptor signaling are extensively involved in regulating gene expression and biological activity in podocytes.[39] They inhibit podocyte apoptosis by modulating the expression of transforming growth factor-β (TGF-β) and angiotensinogen through the nuclear factor-κB (NF-κB) pathway.[40,41] Paricalcitol, a synthetic vitamin D analog, stimulates VDR expression in podocytes and helps to reduce podocyte damage.[42] Additionally, vitamin D is involved in regulating autophagy and promotes autophagic flux in podocytes by up-regulating the expression of ATG16L1.[43] This process is crucial for maintaining podocyte repair and survival. Overall, vitamin D and its analogs play an important role in preserving podocyte health and function.

Vitamin D and Its Receptor Signaling Inhibit The Activation of the Renin-Angiotensin System

Hyperactivation of the renin-angiotensin system (RAS) in patients with diabetic nephropathy leads to hyperglycemia and oxidative stress, which exacerbates renal damage.[44] Elevated levels of angiotensin II (ANG-II) cause renal inflammation, renal cortical damage, and alterations in renal hemodynamics.[45] Vitamin D is a potent negative regulator of the RAS and improves renal function in various kidney disease models by inhibiting renin biosynthesis.[45] Paricalcitol, a vitamin D analog, provides nephroprotection in diabetic mice by inhibiting angiotensin-converting enzyme 2 (ACE2) activity.[46] Additionally, vitamin D supplementation has been shown to significantly reduce the risk of diabetes.[47] Supplementation with vitamin D significantly

inhibited RAS activation in diabetic rats, and combined treatment with chlorthalidone and paricalcitol also reversed diabetes-induced glomerulosclerosis.[47] These findings suggest that modulating RAS hyperactivation may be an important strategy in the prevention and treatment of diabetic nephropathy, particularly through the intervention of vitamin D or its analogs.

Vitamin D and Its Receptor Signaling Inhibit Renal Interstitial Fibrosis

Interstitial fibrosis is a significant contributor to the development of diabetic nephropathy.[48] Vitamin D and its receptor signaling ameliorate renal tubulointerstitial fibrosis by promoting renal tubular cell proliferation, maintaining mitochondrial function, and inhibiting oxidative stress through the Mfn2-MAMs-Fundc1 pathway.[49] Additionally, vitamin D and its receptor signaling inhibit the activation of fibronectin (FN), TGF-β, and the renin-angiotensin-aldosterone system (RAAS), thereby reducing renal tubulointerstitial fibrosis.[50] Vitamin D also blocks the expression of fibrosis-related proteins by inhibiting NF-κB activity and epithelial-mesenchymal transition (EMT).[51] Furthermore, vitamin D reduces the expression of collagen and fibrosis-associated molecules while upregulating MMP8 expression to promote extracellular matrix degradation.[52] These findings suggest that vitamin D has significant potential in combating interstitial fibrosis and protecting renal health, especially in the context of diabetic nephropathy.

POTENTIAL BENEFITS AND ADVERSE EFFECTS OF VITAMIN D AND ITS RECEPTOR SIGNALING IN THE MANAGEMENT OF PATIENTS WITH DIABETIC NEPHROPATHY

Potential Benefits of Vitamin D in the Management of Diabetic Nephropathy

Vitamin D deficiency is considered an important risk factor for the development of diabetic kidney disease (DKD). Studies have shown that serum vitamin D levels are negatively correlated with the risk of diabetic microvascular complications (e.g., retinopathy, nephropathy, neuropathy), and maintaining adequate vitamin D levels may be beneficial in preventing these complications.[53] Low serum vitamin D levels are significantly associated with an increased risk of cardiovascular disease in prediabetic patients.[54] The risk of cardiovascular and cerebrovascular disease is notably elevated in patients with prediabetes.[54] Regular monitoring of serum vitamin D levels is essential to prevent vascular complications. Vitamin D plays a role in slowing the progression of DKD and protecting the integrity of the glomerular filtration barrier.[55] Therefore, clinicians should be vigilant about vitamin D deficiency in patients with DKD and emphasize vitamin D supplementation for high-risk groups.[20] However, there are no definitive recommendations on the optimal dose and timing of vitamin D therapy, and further research is needed to investigate individual differences and the impact on treatment response.

Drug Innovation and the Use of Vitamin D Receptor Agonists

The efficacy of novel drugs in the treatment of diabetic kidney disease (DKD) and their clinical applications have been extensively studied in recent years.[56,57] Paricalcitol, a novel vitamin D analog, is effective in reducing urinary protein levels, inflammatory responses, vascular calcification, and renal fibrosis.[56] Paricalcitol may exert nephroprotective effects by upregulating vitamin D receptor (VDR) expression in renal parenchymal cells and inhibiting fibronectin expression.[57] Osteotriol and paricalcitol also exert therapeutic effects in hemodialysis patients by upregulating VDR expression in immune cells.[58] Additionally, teridol, a selective VDR activator, has been shown to reduce proteinuria and delay the progression of renal injury.[57] Tanshinone has been found to ameliorate renal fibrosis, reduce fasting blood glucose levels, and improve renal function in DKD rats.[59] Combining a VDR activator with a renin-angiotensin system (RAS) inhibitor, such as paricalcitol RAS inhibitor, has been shown to reduce the progression of DKD by increasing the bioavailability of vitamin D.[60,61] This combination therapy strategy offers new directions and prospects for the future clinical management of DKD.

Adverse Effects of Vitamin D and Therapeutic Challenges

Vitamin D can exert significant physiological effects at lower doses, but excessive intake may lead to serious adverse effects, including hypercalcemia, disturbances in calcium and phosphorus metabolism, and even death.[62] In patients with diabetic kidney disease (DKD), vitamin D therapy may trigger adverse effects. This is partly due to historical cases of toxicity from vitamin D overdose in early medical practice. However, available studies suggest that there is a safe range between the optimal dose for maximizing vitamin D status and its toxic dose.[63] Additionally, BsmI VDR gene polymorphisms may be associated with an increased risk of hypercalcemia, highlighting the importance of individualized treatment based on vitamin D status and genetic factors.[64] Patients receiving vitamin D therapy may be more prone to developing hypercalcemia and increased calcium-phosphate product levels.[65,66] In the PRIMO randomized controlled trial, the incidence of hypercalcemia was significantly higher in the paricalcitol-treated group compared to the placebo group.[67] Both the PRIMO and VITAL studies observed a significant decrease in the estimated glomerular filtration rate (eGFR) in the paricalcitol treatment group.[67,68] While this decrease may reflect the effects of conventional RAS inhibitory therapy, it may also be related to changes in creatinine metabolism. Therefore, the efficacy and safety of using vitamin D and its analogs in patients with DKD still require more careful evaluation in future studies. Overall, although vitamin D and its receptor signaling show potential clinical benefits in DKD treatment, their adverse effects and individual variability necessitate a thorough assessment by clinicians when applying vitamin D-related therapies. Exploring rational combination therapy options is essential to achieve better efficacy and safety.

BIBLIOMETRIC ANALYSIS OF RESEARCH HOTSPOTS

Bibliometric Analysis

To reveal the research hotspots and trends related to vitamin D and its receptors in the field of diabetic nephropathy, we utilized VoSviewer (76) and the R package "bibliometrix".[69] We analyzed co-occurring keywords and trending topics in VDR research within nephrology. This study involved analyzing keyword co-occurrence using bibliometric software (**Figure 1**).[70]

Search Strategy and Data Collection

We conducted a literature search using the Web of Science Core Collection (WoS) database (https://www.webofscience.com/wos/woscc/

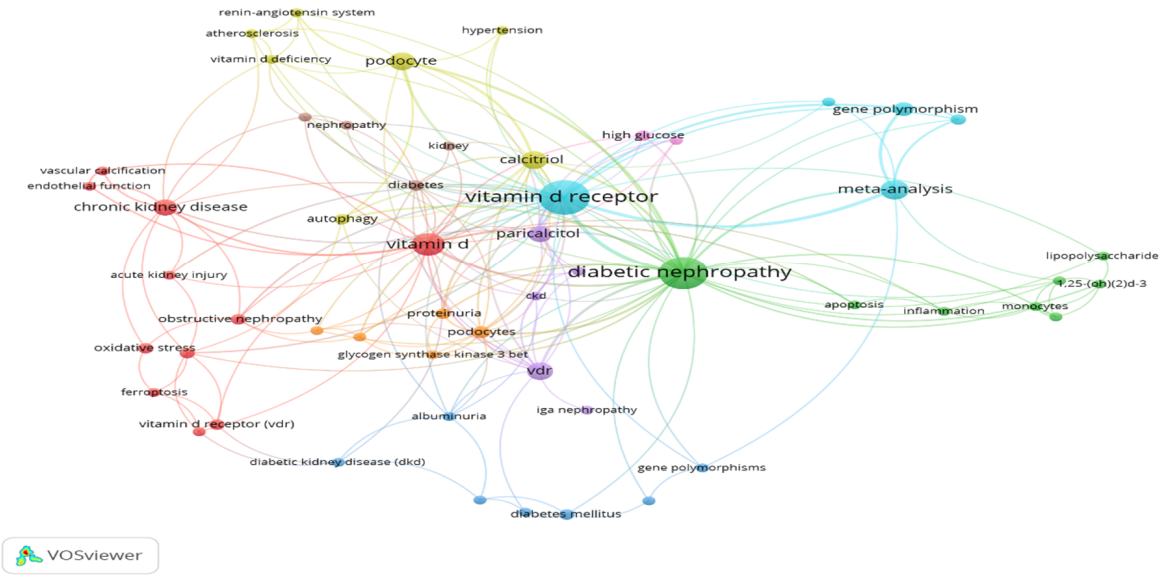

Figure 1. Keyword co-occurrence visualization and analysis map

basic-search). The search strategy was TS = (VDR) AND TS = (Nephropathy) AND LA = (English), with the restricted literature types being "article" and "review". Using this search formula, we collected research literature related to vitamin D receptor (VDR) and nephropathy. VOSviewer is a software commonly used for bibliometric analysis, capable of extracting and constructing collaborative, co-citation, and keyword co-occurrence networks from a large number of publications.[71,72] In the visual graphs generated by VOSviewer, each node represents a research entry, the size of the node indicates the number of entries, and the color is used for classification. The thickness of the connecting lines between nodes reflects the strength of the collaboration or co-citation relationship between the items.[72,73] Additionally, CiteSpace is a bibliometric analysis and visualization tool.[74] In this study, we used CiteSpace to create a biplot overlay of journals (**Figure 4**) and to analyze the emergence of references (**Figure 3**). We also utilized the R package "bibliometrix" (https://www.bibliometrix.org) for topic evolution analysis (**Figure 2**). Furthermore, Microsoft Office Excel 2019 was used to analyze the annual number of publications in the literature (**Figure 5**).

Research Hot Topics and Preface

Table 1 shows the top 20 most frequently occurring keywords in this research area, with

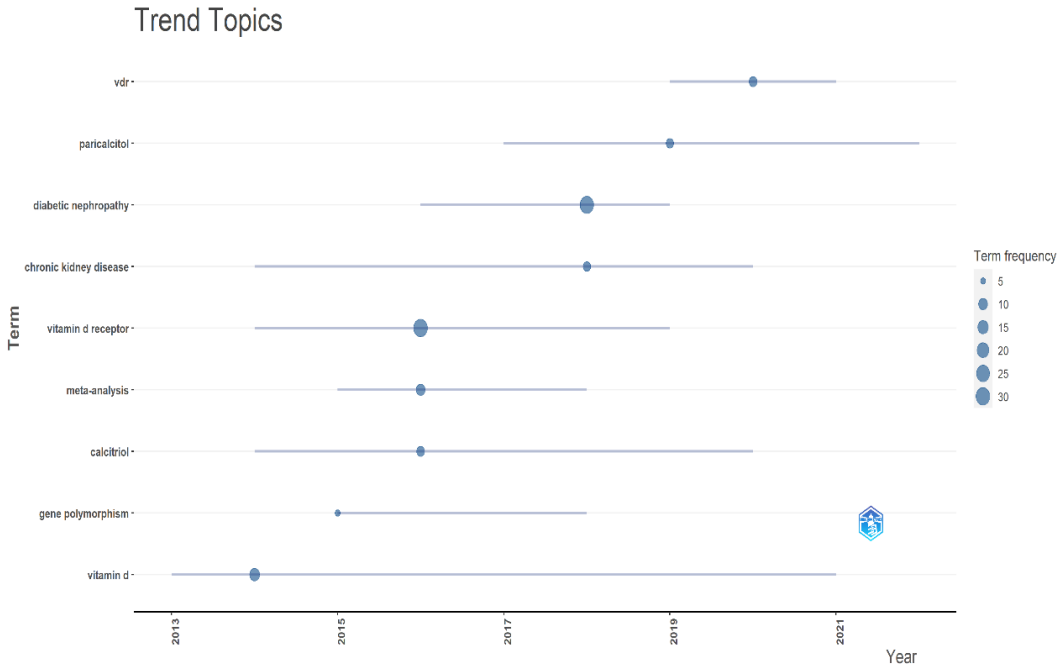

Figure 2. Keyword trend topic analysis chart.

Top 11 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2012 - 2023
de Zeeuw D, 2010, LANCET, V376, P1543, DOI 10.1016/S0140-6736(10)61032-X, DOI	2010	4.67	2012	2014	
Freundlich M, 2008, KIDNEY INT, V74, P1394, DOI 10.1038/ki.2008.408, DOI	2008	3.21	2012	2013	
Zhang Z, 2008, P NATL ACAD SCI USA, V105, P15896, DOI 10.1073/pnas.0803751105, DOI	2008	2.75	2012	2013	
Tan XY, 2008, J AM SOC NEPHROL, V19, P1741, DOI 10.1681/ASN.2007060666, DOI	2008	2.75	2012	2013	
Zhang Z, 2008, KIDNEY INT, V73, P163, DOI 10.1038/sj.ki.5002572, DOI	2008	2.75	2012	2013	
Alborzi P, 2008, HYPERTENSION, V52, P249, DOI 10.1161/HYPERTENSIONAHA.108.113159, DOI	2008	2.75	2012	2013	
Zhang H, 2012, GENE, V495, P183, DOI 10.1016/j.gene.2011.12.049, DOI	2012	2.58	2014	2017	
Yang SK, 2018, CURR MED CHEM, V25, P3256, DOI 10.2174/0929867325666180214122352, DOI	2018	2.91	2019	2023	
Yang LN, 2017, BMC MED GENET, V18, P0, DOI 10.1186/s12881-017-0458-8, DOI	2017	2.77	2019	2020	
Guo J, 2017, CELL PHYSIOL BIOCHEM, V43, P39, DOI 10.1159/000480315, DOI	2017	2.59	2019	2021	
Lei M, 2020, BIOMED RES INT, V2020, P0, DOI 10.1155/2020/4137268, DOI	2020	2.63	2021	2023	

Figure 3. Reference emergence map

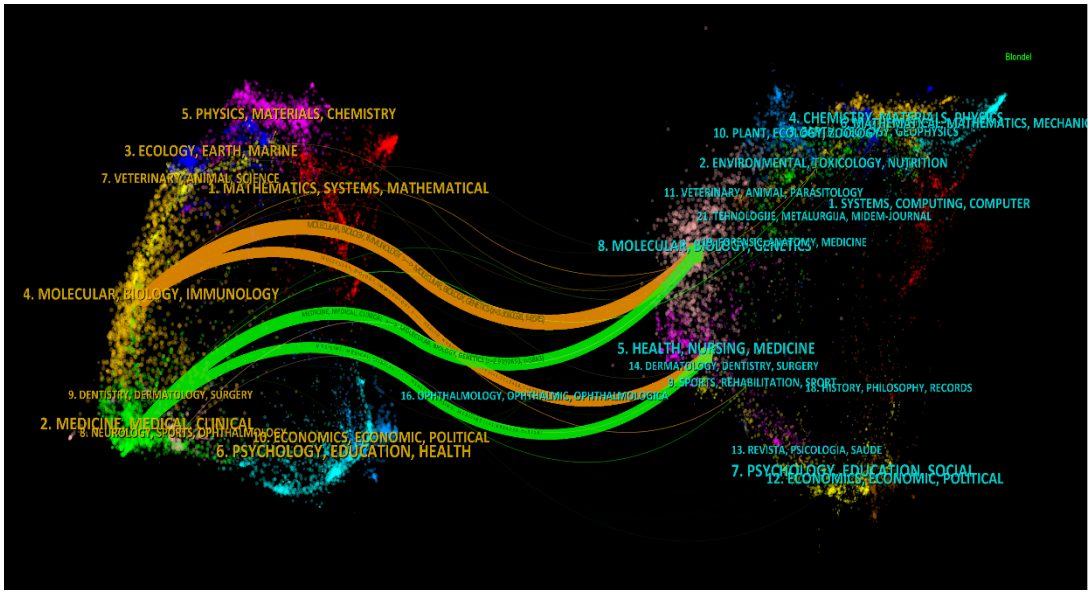

Figure 4. Journal double image overlay

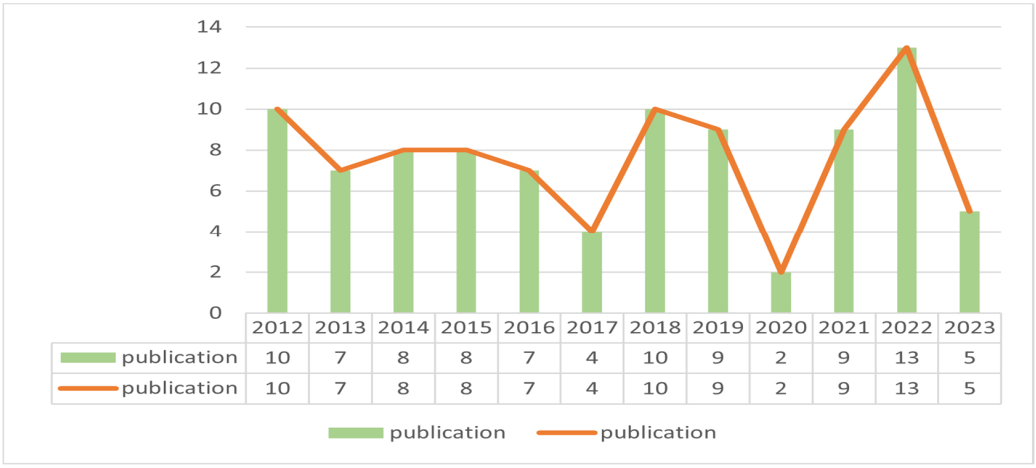

Figure 5. Graph of the volume of communications

"vitamin D receptor" appearing more than 30 times. We filtered the keywords with ≥2 occurrences and performed cluster analysis using VOSviewer (**Figure 1**). In the visual graph, the thicker the connecting lines between nodes, the stronger the correlation between keywords. The analysis revealed that "vitamin D receptor," "vitamin D," and "diabetic nephropathy" have a strong correlation with each other. The thematic analysis of keyword trends (**Figure 2**) showed that between 2013 and 2016, studies predominantly focused on "vitamin D" and related "meta-analysis," with core keywords being "vitamin D receptor" and "calcitriol." Since 2017, researchers have gradually shifted their focus to exploring the pathogenesis and therapeutic potential of the vitamin D receptor (VDR) in diabetic nephropathy, with keywords including "VDR," "paricalcitol," and "diabetic nephropathy". In conclusion, the literature search and data analysis indicate that the study of the vitamin D receptor and diabetic nephropathy is both promising and scientifically valuable. Future research should further advance relevant clinical trials and promote the practical application of these theories in treatment.

Table 1. Top 20 keywords in research

Rank	Keywords	Counts	Rank	Keywords	Counts
1	vitamin d receptor	30	11	podocytes	4
2	diabetic nephropathy	28	12	diabetes	3
3	vitamin D	13	13	autophagy	3
4	meta-analysis	10	14	proteinuria	3
5	ver	8	15	renal tubular epithelial cell	3
6	calcitriol	8	16	high glucose	3
7	podocyte	8	17	nephrolithiasis	3
8	chronic kidney disease	7	18	Obstructive nephropathy	3
9	paricalcitol	7	19	ckd	3
10	gene polymorphism	5	20	albuminuria	2

Reference Highlighting

As shown in **Figure 3**, this study analyzes reference bursts, where each bar represents a year, and the red bars indicate periods of strong citation bursts that occurred in that year.[75] The earliest citation bursts began in 2008, with the most recent occurring in 2020. The literature with the highest citation burst intensity was authored by de Zeeuw D et al., with a burst intensity of 4.67 and citation bursts occurring from 2014 to 2018. Following this, the work by Freunlich M et al. had a burst intensity of 3.21, with citation bursts from 2013 to 2016. Overall, these 11 pieces of literature with citation bursts exhibited burst intensities ranging from 2.63 to 4.67, with burst durations spanning from 2 to 5 years. This analysis indicates that certain literature has had a more significant impact on the research field during specific periods, reflecting the research hotspots and focus of attention at different stages.

Journal Double Figure Overlay

The double plot overlay of journals illustrates the citation relationships between citing journals and co-cited journals. In **Figure 4**, the left side represents the cluster of citing journals, while the right side represents the cluster of cited journals. The orange paths indicate the major citation pathways, showing that research published in journals within the fields of molecular biology and immunology is primarily cited by literature in molecular biology and pharmacology journals. This analysis highlights patterns of knowledge flow and citation across different subject areas, contributing to a better understanding of the interdisciplinary impact of vitamin D and its receptors in diabetic nephropathy research.

Statistics on the Volume of Publications

According to our search strategy (**Figure 5**), a total of 92 studies on vitamin D receptor (VDR) and nephropathy were retrieved over the past two decades, including 77 "Articles" and 15 "Reviews." The trend in the annual number of publications shows a significant increase in 2012, 2018, and 2022, with decreases observed in 2017 and 2020. The relatively low overall number of publications suggests that the field still requires further research to advance its development and clinical application.

CONCLUSION

Vitamin D and its receptor signaling play a crucial protective role in the pathogenesis of diabetic kidney disease (DKD). By modulating the inflammatory response, reducing oxidative stress, and inhibiting renal fibrosis, vitamin D and its receptor have significant potential to intervene in the development and progression of DKD. Vitamin D supplementation or the use of vitamin D receptor agonists has been shown to delay the deterioration of renal function and improve clinical outcomes in patients with DKD. However, existing studies remain uncertain regarding the optimal therapeutic dose, long-term efficacy, and potential side effects. Future research should aim to define the optimal vitamin D treatment regimen and optimize its safety and efficacy in clinical settings. Additionally, bibliometric analyses indicate that research hotspots related to vitamin D receptor signaling in DKD therapy are becoming more focused, providing a crucial foundation for exploring novel therapeutic approaches. In conclusion,

modulation of vitamin D and its receptor signaling pathways is a promising strategy for treating diabetic nephropathy, but more in-depth clinical and basic studies are needed to validate its comprehensive efficacy.

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DATA AVAILABILITY

Data supporting the findings of this study are available from the article.

ETHICAL APPROVAL

Since the data from published studies were used for the study, there was no need for additional ethical approval.

INFORMED CONSENT

All analyses were performed using publicly available datasets. The studies cited in this research have received approval from their respective ethical review boards and have complied with informed consent requirements from participants.

COMPETING INTEREST

The authors declare no competing interests.

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