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Review

Role of polymorphism in vitamin D receptor gene on diabetic foot ulcer: A systematic review and meta-analysis

[Papel del polimorfismo del gen receptor de la vitamina D en la úlcera del pie diabético: Una revisión sistemática y meta-análisis]

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Abstract

Context: Once vitamin D is converted to its active form, the molecule binds to its receptor (VDR) and performs its function as a transcription factor in modulating immune response, inflammation cascade, and insulin signaling. Among diabetic individuals, these activities are thought to be correlated with foot ulceration. Gene polymorphisms could change the function of VDR, thereby affecting the development of foot ulceration among individuals with diabetes.

Aims: To construct evidence on the role of VDR gene variants or single nucleotide polymorphisms (SNPs) on diabetic foot ulcers.

Methods: Records reporting the distribution of genotypes and/or alleles among diabetic foot ulcer (DFU) patients and published until 10 March 2023 were retrieved from 12 major databases using predetermined keywords. The original research articles included in the study were assessed for reporting quality using the Newcastle Ottawa Scale. The quality of genotypic and allelic data was appraised by Hardy-Weinberg equilibrium (HWE). A quantitative analysis-based fixed-effects model was performed to estimate the proportion of genotype and allele frequencies among DFU patients.

Results: Three studies were included in the systematic review reporting the FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) SNPs. Based on pooled estimates, among DFU patients CC, CT, and TT genotypes of VDR FokI SNPs had a prevalence of 45%, 43%, and 12%, respectively, without significant heterogeneity found in the reported data (p-Het<0.001; I^2>0%). ApaI and FokI were associated with DFU, while no association in all genotypic and allelic models was found between TaqI or BsmI and DFU. CC genotype of BsmI and T allele of FokI was associated with oxidative stress (one of the underlying factors in DFU).

Conclusions: Certain genotypes and alleles of FokI and ApaI SNPs could act as the risk factor for foot ulceration among diabetic individuals. More high-quality studies are still needed to draw solid conclusions on the role of VDR SNPs among DFU patients.

Keywords: diabetic complications; diabetic foot; gene variants; vitamin D; vitamin D receptor.

Resumen

Contexto: Una vez que la vitamina D se convierte en su forma activa, la molécula se une a su receptor (VDR) y desempeña su función como factor de transcripción en la modulación de la respuesta inmunitaria, la cascada de la inflamación y la señalización de la insulina. Entre los individuos diabéticos, se cree que estas actividades están correlacionadas con la ulceración del pie. Los polimorfismos genéticos podrían cambiar la función de VDR, afectando la aparición de úlceras en los pies de los diabéticos.

Objetivos: Construir evidencias sobre el papel de las variantes del gen VDR o polimorfismos de nucleótido único (SNPs) en las úlceras del pie diabético.

Métodos: Los registros que informan sobre la distribución de genotipos y/o alelos entre los pacientes con úlcera de pie diabético (UPD) y publicados hasta el 10 de marzo de 2023 se recuperaron de 12 bases de datos principales utilizando palabras clave predeterminadas. Se evaluó la calidad de los informes de los artículos de investigación originales incluidos en el estudio mediante la escala de Newcastle Ottawa. La calidad de los datos genotípicos y alélicos se evaluó mediante el equilibrio de Hardy-Weinberg (HWE). Se realizó un modelo de efectos fijos basado en el análisis cuantitativo para estimar la proporción de las frecuencias genotípicas y alélicas entre los pacientes con DFU.

Resultados: Se incluyeron tres estudios en la revisión sistemática que informaban sobre los SNP FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410) y ApaI (rs7975232). Según las estimaciones agrupadas, entre los pacientes con DFU los genotipos CC, CT y TT de los SNP VDR FokI tenían una prevalencia del 45%, 43% y 12%, respectivamente, sin que se encontrara heterogeneidad significativa en los datos comunicados (p-Het<0,001; I^2>0%). ApaI y FokI se asociaron con DFU, mientras que no se encontró asociación en todos los modelos genotípicos y alélicos entre TaqI o BsmI y DFU. El genotipo CC de BsmI y el alelo T de FokI se asociaron con el estrés oxidativo (uno de los factores subyacentes en el DFU).

Conclusiones: Ciertos genotipos y alelos de los SNP de FokI y ApaI podrían actuar como factor de riesgo de ulceración del pie entre los individuos diabéticos. Todavía se necesitan más estudios de alta calidad para extraer conclusiones sólidas sobre el papel de los SNP VDR entre los pacientes con DFU.

Palabras Clave: complicaciones diabéticas; pie diabético; variantes génicas; vitamina D; receptor de la vitamina D.

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INTRODUCTION

Diabetic patients are at risk of developing foot ulceration that might lead to lower extremity amputations (Lazzarini et al., 2023; McDermott et al., 2023). The disease is more common among men, and higher risks are found in those with a smoking habit, long diabetes duration, older age, increased body mass index, and diabetic cardiovascular complications (Ansari et al., 2022; Zhang et al., 2017). Recently, serum vitamin D has been thought to be a novel risk factor for diabetic foot ulcer (DFU), as suggested by two systematic reviews (Lin et al., 2023; Yammine et al., 2020). Furthermore, a research group from China found that vitamin D deficiency might predict all-cause mortality among individuals with DFU (Tang et al., 2023a). However, it is still unclear whether a lower level of serum vitamin D (SVD) has a causal relationship with DFU or just a mere confounding (Greenhagen et al., 2019). For example, people with DFU tend to have fewer outdoor activities due to their mobility constraints, which causes them to have lower exposure to sunlight (Lips et al., 2019; Tsitsou et al., 2023). Lower levels of SVD can also be caused by diabetic nephropathy since kidneys are organs that primarily convert vitamin D to its active form (cholecalciferol) through hydroxylation (Greenhagen et al., 2019).

Previously, vitamin D was known as a regulator for calcium hemostasis, playing a role in bone formation and mineralization. However, recent knowledge on vitamin D receptor (VDR) being expressed in pancreatic beta cells and macrophages, among other cells, suggests that the vitamin is more than just a calcium regulator (Osmani and Haseena, 2020; Yaribeygi et al., 2020). The complex formed between vitamin D and its receptor can act as a transcription factor that consequently affects the immune system and regulation of inflammatory response (Bhatti et al., 2022; Yaribeygi et al., 2020). Some antibacterial peptides are expressed following the initiation of this complex (Ismailova and White, 2022). It is also possible for vitamin D to improve the sensitivity and function of insulin (Yaribeygi et al., 2020), though conflicting results are found in randomized clinical trials (RCTs) (Pieńkowska et al., 2023). Taken altogether, there is a huge possibility that vitamin D and its receptor are correlated with DFU.

VDR has several single nucleotide polymorphisms (SNPs) that can affect the receptor functions, including those related to diabetic complications. FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) are among the known SNPs that have been found to be correlated with immune dysregulation (Maalmi et al., 2013; Nejentsev et al., 2004; Rose et al., 2013; Saadi et al., 2009; Whitfield et al., 2001; Zmuda et al., 2000). In a meta-analysis, BsmI, ApaI, and FokI genetic variants were found to be associated with vascular complications in diabetes (Song et al., 2019). Therefore, the SNPs were thought to be associated with foot ulceration among diabetic patients. Previously, a systematic review has been performed on DFU-associated gene variants, but it did not focus on VDR genes (Zhao et al., 2022). There is still little evidence on the role of SNPs, particularly in VDR genes, and some studies reported conflicting results (Khalshami et al., 2022; Raflis et al., 2020; Soroush et al., 2017; Zhao et al., 2022). Moreover, the previous review was not sufficient to synthesize the evidence on the role of vitamin D in the development of DFU. In addition, the previous review did not perform quantitative analysis on the prevalence of VDR gene variants. These analyses are important for risk factor stratification, early detection of DFU, and personalized medical treatment. As the first to report, this systematic review aimed to collect evidence of VDR gene variants among DFU patients (as compared to diabetic patients without DFU) and their roles in the development of the disease.

MATERIAL AND METHODS

Research objectives and design

The objective was to assess the association between polymorphism in the vitamin D receptor gene and foot ulceration incidences in non-gestational diabetic patients. Examples of the polymorphism included FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232). The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The protocols were preplanned and registered in PROSPERO (CRD42023424019). See Tables S1-S2.

Search strategy

The literature search was performed on 10 March 2023, using the search engine from the following databases: PubMed, Scopus, Embase, Scillit, Sci-Finder, LILACS, EuropePMC, medRxiv, bioRvix, Research Square, Google Scholar, and Garuda. Keywords "Diabetes", "Foot Ulcer", and "Vitamin D", as well as their respective synonyms, were used in combinations as presented in Table S3.

Inclusion and exclusion criteria

To set the eligibility criteria, this study employed the PECOS (Population, Exposure, Control, and Out-

comes) framework. The population was diabetic patients, while the exposure was DFU. Control, if any, was diabetic patients without foot ulcers. Studies reporting the distribution of genotypes and/or alleles as outcomes among DFU patients were included. We included observational (retrospective/prospective) and case-control studies. Articles published as literature reviews, commentaries, editorials, case reports, erratum, and conference abstracts were not included. English or Indonesian language were the language restrictions.

Screening and selection of the records

PRISMA guideline was adopted for the screening as well as the selection process performed independently by M.I and N.G. Duplication on the retrieved records from the database was removed automatically by Mendeley Desktop v1.19.8 (https://www.mendeley.com/). Thereafter, the title and abstract of each record were screened. Records passing the initial screening would undergo a full-text review in which the criteria for inclusion or exclusion were applied. Different results from these screening steps would be overcome by revisiting the article, and the consensus would be reached by discussion. Consultation with another reviewer (S.A.) would be required if a consensus could not be reached.

Study quality assessment

The Newcastle Ottawa Scale was used to assess the quality of the included studies. Two independent reviewers carried out this assessment – M.I. and S.A. Studies receiving a total score of ≥7 were considered high quality. Hardy-Weinberg equilibrium (HWE) was measured for genotype and allele frequencies.

Data extraction

The first author's name, year of publication, the study location (country), study design, and sample size were collected. Patients' characteristics, including the type of diabetes, age, sex, diabetes onset, body mass index, and glycated hemoglobin (HbA1c) level were extracted from each study. Genotype frequency and/or minor allele frequency were extracted. Continuous data were presented as mean ± standard deviation (SD), while ordinal was presented as frequency (%). Data presented as median were converted to mean (https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html). No conversion was performed for data presented in different units; the standardized mean difference (SMD) would be used in the data analysis.

Statistical analysis

In this present study, Jamovi version 2.3.21 (https://www.jamovi.org/) was employed for the meta-analysis. A fixed-effects model was applied to obtain a raw genotype and allele frequency proportion. The heterogeneity of the pooled data was judged based on I^2, where the values of <25%, 26-50%, and >50% indicate low, moderate, and high heterogeneity levels. For analyzing the impact of vitamin D deficiency on the occurrence of diabetic foot ulcers, we used odd ratio (OR) and 95% confidence intervals (CIs). The threshold for statistical significance was $p<0.05$. Publication bias would be assessed through Begg's funnel plot if the number of studies was equal or greater than 10, as suggested by previous studies (Duta et al., 2023; Kurniawan and Hariyanto, 2023).

RESULTS

Searching results

We found as many as 4441 documents in the initial identification through twelve different databases, which were then enlisted 3391 records for the next selection steps after automatic duplicate removal. By screening the title and abstract, 79 records were further found to be potentially relevant to the present review. Out of these, 40 were excluded due to irrelevance to the study. Eleven articles were mere conference abstracts or editorials, hence excluded. A large portion (n = 25) of the excluded studies in the full-text screening was from studies that only reported vitamin D levels in serum or VDR (such as (Kanwal et al., 2022; Priyanto et al., 2023; Tang et al., 2023b). A study reported VDR BsmI SNP, but the sample was not specified for DFU (Hong et al., 2015). Finally, three studies met the eligibility criteria and were included (Klashami et al., 2022; Raflis et al., 2020; Soroush et al., 2017). A summary of the search and selection process in a flow diagram is presented in Fig. 1.

Characteristics of included studies

We found three studies to be included: two used case-control study design, and one used cross-sectional. The studies were conducted in the following countries: Iran (two studies) and Indonesia (one study). Most of the patients were between 40 and 60 years old. Duration of diabetes was around 13-15 years, with HbgA1C around 7-8. Detailed characteristics of the studies are presented in Table 1.

Quality of included studies

Quality appraisal of the selected studies is presented in Table 2. Two studies received an overall score of nine, indicating their low risk of bias

(Klashami et al., 2022; Soroush et al., 2017). A study received an overall score of four, suffering from the lack of comparability and exposure (Raflis et al., 2020). All studies were deviated from HWE equation (Klashami et al., 2022; Raflis et al., 2020; Soroush et al., 2017).

Prevalence of genotypes of VDR SNPs

Pooled estimates of the prevalence of each SNP genotype of VDR FokI among DFU patients have been presented in Fig. 2. CC and CT genotypes had similar prevalence that reached 45% and 43%, respectively. In combination with the dominant model (CC + CT), the genotype had a prevalence of 88%. TT genotype had a prevalence of 12%. Notably, the prevalence for CC, CT, CC + CT, and TT was reported homogenously (p-Het<0.001; I^2>0%).

Qualitatively, the CC genotype and C allele of FokI were more prevalent among control than that of DFU individuals (61% vs. 47% and 68% vs. 78%, respectively). Meanwhile, the T allele of FokI had a higher frequency in DFU patients than in diabetic patients (32% vs. 22%). For ApaI, GG appeared more frequent in diabetic patients without DFU than in the DFU group (13% vs. 2%). The distribution of genotypes and alleles of TaqI and BsmI were not significantly different between case and control groups.

Association of VDR SNP and diabetic foot ulcer

TaqI and BsmI were not associated with DFU in all genotypic and allelic models (Klashami et al., 2022). The association of ApaI and DFU was found to be significant, and its GG genotype was specifically associated with oxidative stress in the patients' plasma (Klashami et al., 2022). Association with oxidative stress was also found for the CC genotype of BsmI (Klashami et al., 2022). In the case of FokI, the TT genotype of the polymorphism is strongly associated with DFU, whereas the T allele is associated with oxidative stress (Soroush et al., 2017). See Table 3.

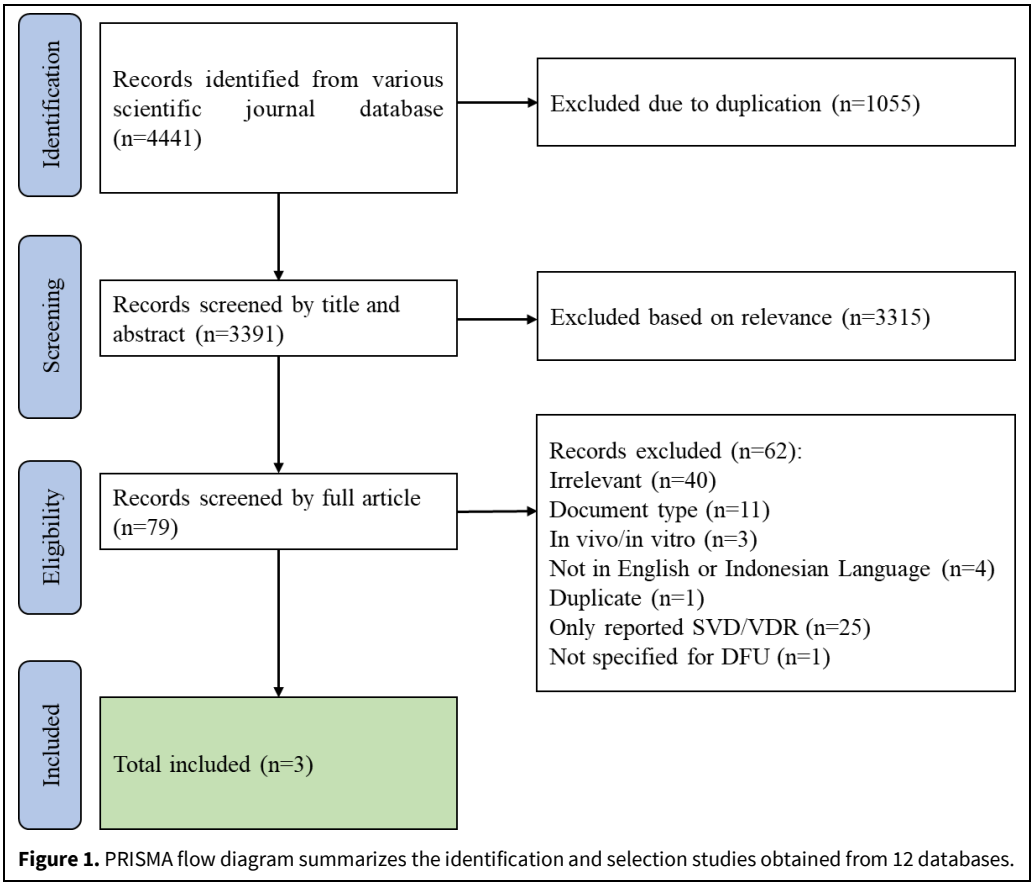

Figure 1. PRISMA flow diagram summarizes the identification and selection studies obtained from 12 databases.

Table 1. Characteristics of included studies.

Author (year)	Country (study design)	Subjects			Age, Mean ± SD (years)	Duration of diabetes, Mean ± SD (years)	HbA1C, Mean ± SD (%)
		Control (n)	Case (n)	Male (%)			
Soroush et al., 2017	Iran (case-control)	207	105	46.2	Case: 56 ± 7.8 Control: 55.9 ± 6.6	Case: 15.4 ± 6.9 Control: 13.1 ± 6.4	Case: 8.0 ± 1.2 Control: 7.7 ± 1.2
Klashami et al., 2022	Iran (case-control)	135	127	37.4	Case: 56 ± 7.8 Control: 55.9 ± 6.6	Case: 15.4±6.9 Control: 13.1±6.4	Case: 8.0 ± 1.2 Control: 7.7 ± 1.2
Raflis et al., 2020	Indonesia (cross-sectional)	-	36	47.2	40-65 years old (range)	No information	No information

Table 2. Quality of included studies.

ID	Study design	Selection	Comparability	Exposure	Overall score
Soroush et al., 2017	Case-control	☆☆☆☆	☆☆	☆☆☆	9
Klashami et al., 2022	Case-control	☆☆☆☆	☆☆	☆☆☆	9
Raflis et al., 2020	Cross-sectional	☆☆☆	Not applicable	☆	4

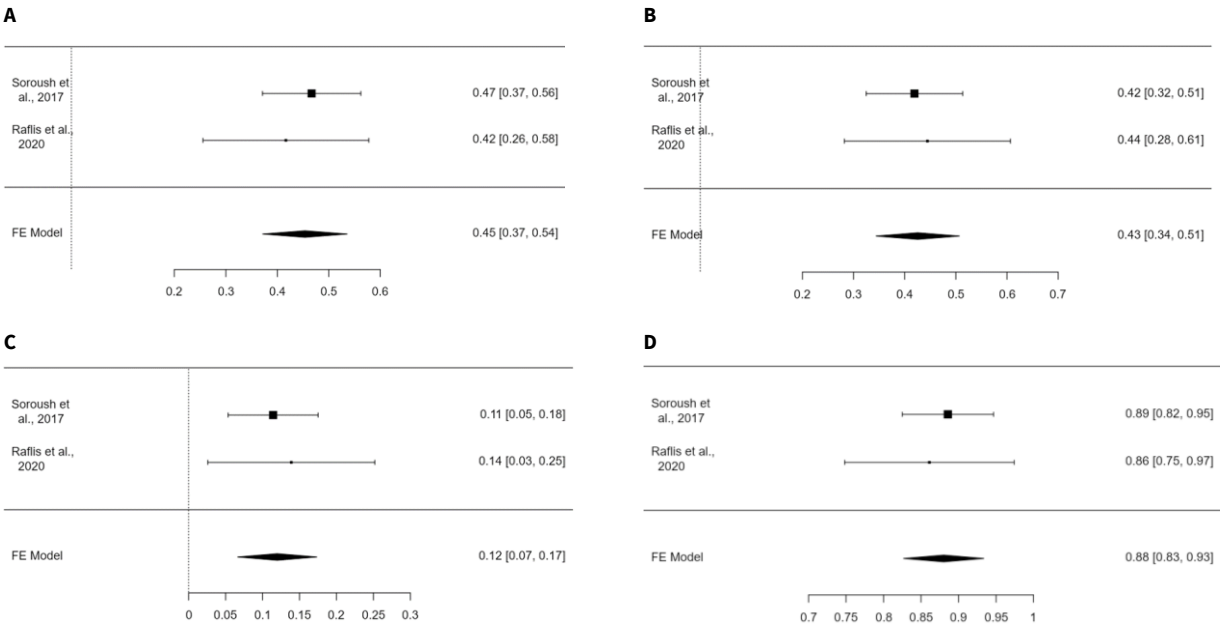

Figure 2. Pooled estimates of VDR FokI genotypes and alleles prevalence among DFU patients.

(A) CC (p<0.001; 45% [95%CI: 37%–54%]); p-Het<0.001, I^2=97%. **(B)** CT (p<0.001; 43% [95%CI: 34%–51%]); p-Het=0.791, I^2=0%. **(C)** TT (p<0.001; 12% [95%CI: 7%–17%]); p-Het=0.707, I^2=0%. **(D)** CC + CT (p<0.001; 88% [95%CI: 83%–93%]); p-Het=707, I^2=0%.

DISCUSSION

VDR is expressed in macrophages, endothelial cells, and smooth muscle cells, suggesting its implications for pathologic conditions related to vascular diseases and inflammation (Burgaz et al., 2011). The complex of VDR and activated vitamin D (cholecalciferol) acts as a transcription factor that maintains the balance of anti- and pro-inflammatory proteins (Kurian et al., 2021). Moreover, VDR is responsible for initiating the production of antimicrobial peptides during viral or bacterial infection. In the case of diabetes, patients are susceptible to developing complications, including foot ulceration, derived from dysregulated systemic inflammation and infection. Therefore, the SNPs in VDR must be thought to impact the

Table 3. Distribution of genotypes and alleles of VDR SNPs.

VDR SNP	ID	Case								Control							
		Genotype				Allele			HWE	Genotype				Allele			HWE
		AA	AB	BB	*n*	A	B	*n*		AA	AB	BB	*n*	A	B	*n*	
		CC	CT	TT		C	T			CC	CT	TT		C	T		
FokI (rs2228570)	Soroush et al., 2017	49	44	12	105	142	68	210	0.194	65	36	6	107	166	48	214	0.177
	Raflis et al., 2020	15	16	5	36	-	-	-	NA	-	-	-	-	-	-	-	NA
TaqI (rs731236)	Klashami et al., 2022	10	22	28	127	42	78	254	40.133	14	47	36	135	75	119	270	10.759
BsmI (rs1544410	Klashami et al., 2022	45	56	17	127	146	90	254	0.642	53	64	22	135	170	108	270	0.247
		GG	GC	CC		G	C			GG	GC	CC		G	C		
ApaI (rs7975232)	Klashami et al., 2022	3	41	17	127	47	75	254	56.596	18	53	25	135	89	103	270	12.902

NA: not applicable.

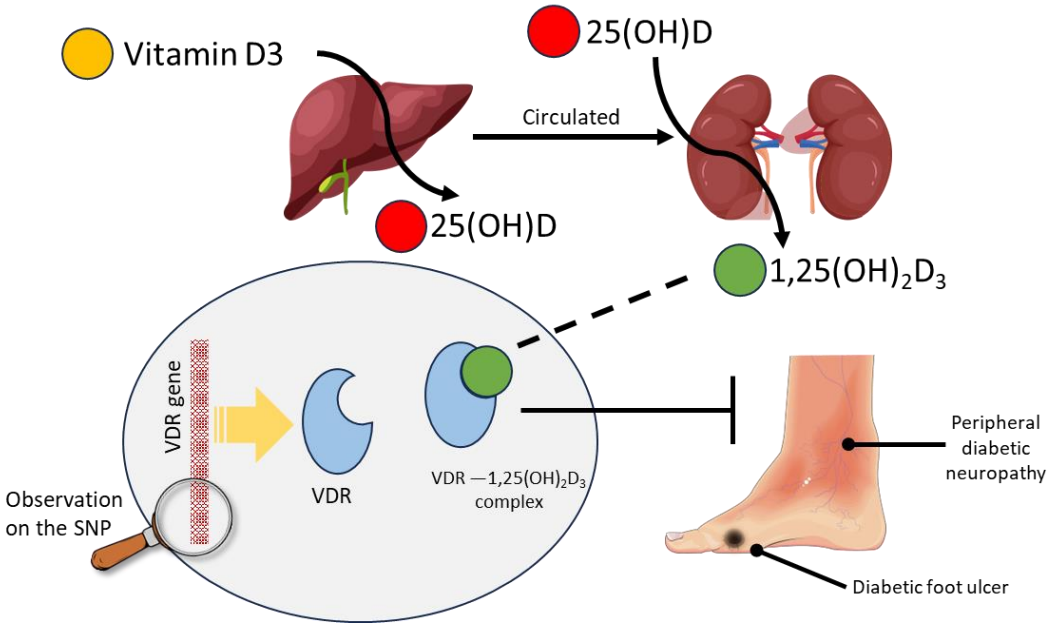

Figure 3. Schematic illustration of vitamin D biosynthesis and its complexation with its receptor (VDR).

Vitamin D3 obtained from the sunlight-facilitated synthesis and intestinal absorption was hydroxylated in the liver to produce 25(OH)D, which is then hydroxylated once again into $1,25(OH_2)D_3$ before re-circulated and bound to vitamin D receptor (D). Genes encoding the protein are present in multiple cells, including macrophages, endothelial cells, and smooth muscle cells. Vitamin D and VDR complex regulate immune cells, inflammatory response and improve insulin sensitivity, which consequently helps prevent peripheral diabetic neuropathy (DPN) and diabetic foot ulcer (DFU). However, these activities might be influenced by the single nucleotide polymorphism (SNP) in the VDR gene. The study is focused on the association between VDR gene SNPs and the risk of DFU.

expression or activity of VDR that consequently affects diabetic patients. The schematic illustration of the association between VDR gene SNP and the risk of DFU is presented in Fig. 3.

Based on the qualitative analysis in this systematic review, gene variants in TaqI and BsmI were not associated with DFU occurrence among diabetic patients (Klashami et al., 2022). Significant associations, however, were found between ApaI as well as FokI SNPs and DFU (Klashami et al., 2022; Soroush et al., 2017). Our data complement the previous meta-analysis focusing on patients with DFU that only identified VDR FokI VDR (Zhao et al., 2022). In a previous meta-analysis, ApaI and FokI gene variants among individuals with diabetes are correlated with a higher risk of developing microvascular complication, such as diabetic nephropathy (Song et al., 2019). As FokI is located in the initial codon (ATG) of the receptor protein, the SNP can cause a change in molecule size by producing C variants (Valdivielso and Fernandez, 2006). Comparatively, ApaI is a silent polymorphism and functions as an mRNA stabilizer (Usategui-Martín et al., 2022). FokI, along with ApaI, have been reported to modulate vitamin D expression (Li et al., 2012). Taken together, these are evidence that ApaI and FokI SNPs are functional polymorphisms in terms of DFU and implicate the activity of VDR.

Previous research has revealed the relationship between vitamin D deficiency and DFU occurrence (Iqhrammullah et al., 2024; Kinesya et al., 2023; Li et al., 2023). Vitamin D and VDR complex could protect the vascular system from inflammatory stress by compressing the activity of the renin–angiotensin–aldosterone system (Li et al., 2002). As a transcription factor, the complex could promote the expression of anti-inflammatory cytokines and simultaneously inhibit the expression of pro-inflammatory cytokines (Gu et al., 2022; Yin and Agrawal, 2014). In several studies, hypovitaminosis D was associated with an increased level of C-reactive protein, erythrocyte sedimentation rate, C—C chemokine 2 (CCL2), interleukin (IL)-1β, IL-6, interferon (IFN)-γ and tumor necrosis factor (TNF)-α (Afarideh et al., 2016; Dai et al., 2020; Tang et al., 2023b; Tiwari et al., 2014; Tsitsou et al., 2023). Reversed inflammation could be achieved through six-month vitamin D supplementation, as observed in the levels of IL-18, TNF-α, and IFN-γ (Johny et al., 2022). Moreover, vitamin D levels in the blood could predict culture-positive diabetic infection (Greenhagen et al., 2019; Tiwari et al., 2014). In a study, the conversion of vitamin D into its active form through hydroxylation in macrophages reveals the

vitamin's role in promoting the production of antimicrobial peptides (Ismailova and White, 2022).

As a limitation of this study, a pooled analysis of the association between VDR SNP and DFU could not be performed because of the lack of data. All the studies reporting the association between VDR polymorphisms and DFU were from a single research group from Iran. Reports from different parts of the world are encouraged as VDR acts differently across ethnicities. In addition, we did not contact relevant experts for unpublished findings or search for potential records on the websites of well-known research institutions, which can result in selection bias altogether. The source of heterogeneity was also not analyzed. The data herein is not conclusive owing to the deviation in HWE. High-quality data should be produced in the future to gain solid conclusions regarding the role of VDR SNPs in foot ulceration among diabetic patients. Understanding the function of these polymorphisms could help establish early diagnosis and precision medicine modalities.

CONCLUSION

The current body of evidence indicatively suggests that certain genotypes and alleles of FokI and ApaI SNPs could be the risk factor for developing DFU among diabetic patients. No association has yet been found for BsmI and TaqI polymorphisms. However, the current evidence is insufficient to draw solid conclusions to determine whether these polymorphisms act as risk factors. Therefore, more studies to investigate the functionality of these polymorphisms in DFU should be further carried out.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Saminan S	Gusti N	Amirah S	Iqhrammullah M
Concepts or ideas	x			x
Design	x			x
Definition of intellectual content	x	x	x	x
Literature search		x	x	
Experimental studies		x	x	
Data acquisition	x	x	x	x
Data analysis		x	x	
Statistical analysis	x			x
Manuscript preparation	x			x
Manuscript editing	x			x
Manuscript review	x	x	x	x

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Supplementary data

Tabe S1. PRISMA 2020 item checklist.

Section and topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Research objectives and design
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Inclusion and exclusion criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Research objectives and design
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Inclusion and exclusion criteria
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Screening and selection of the records
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Data extraction
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Data extraction
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Study quality assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Statistical analysis

Tabe S1. PRISMA 2020 item checklist (continued...)

Section and topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Inclusion and exclusion criteria
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Data extraction
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Statistical analysis
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Statistical analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Statistical analysis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Statistical analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Statistical analysis
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Statistical analysis
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Searching results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Searching results
Study characteristics	17	Cite each included study and present its characteristics.	Characteristics of included studies
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Quality of included studies
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Prevalence of genotypes of VDR SNPs
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Prevalence of genotypes of VDR SNPs

Tabe S1. PRISMA 2020 item checklist (continued...)

Section and topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Quality of included studies
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	D
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Research objectives and design
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Research objectives and design
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Conflict of interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Underlying data.

From: Page et al. (2021).
For more information, visit: http://www.prisma-statement.org/

Table S2. PRISMA 2020 for Abstracts checklist.

Section and topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
Background			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g., databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias		Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results		Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	3	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	4	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence		Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation		Provide a general interpretation of the results and important implications	Yes
OTHER			
Funding		Specify the primary source of funding for the review.	Yes
Registration		Provide the register name and registration number.	Yes

From: Page et al. (2021).

Table S3. Keyword combinations used in different scientific journal databases.

Database	Field	Keyword combination
Scopus, Embase	Title	(T2DM OR T1DM OR Diabet*) AND ("foot ulcer*" OR "feet ulcer" OR "feet wound" OR "foot wound" OR "feet infection" OR "foot infection" OR Complication*) AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxyvitamin D" OR nutri*)
PubMed	Title	(T2DM OR T1DM OR Diabetes OR Diabetic) AND ("foot ulcer*" OR "feet ulcer" OR "feet wound" OR "foot wound" OR "feet infection" OR "foot infection" OR Complication) AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxyvitamin D" OR nutrient OR nutrition)
Scillit	All	(T2DM OR T1DM OR Diabetes OR Diabetic) AND ("foot ulcer*" OR "feet ulcer" OR "feet wound" OR "foot wound" OR "feet infection" OR "foot infection" OR Complication) AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxyvitamin D" OR nutrient OR nutrition)
Sci-Finder	All	(T2DM OR T1DM OR Diabetes OR Diabetic) AND ("foot ulcer*" OR "foot wound" OR OR "foot infection" OR Complication) AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxyvitamin D")
LILACS	All	(T2DM OR T1DM OR Diabetes OR Diabetic) AND ("foot ulcer*" OR "feet ulcer" OR "feet wound" OR "foot wound" OR "feet infection" OR "foot infection" OR Complication) AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxyvitamin D" OR nutrient OR nutrition)
EuropePMC	Title	(T2DM OR T1DM OR Diabetes OR Diabetic) AND ("foot ulcer" OR "foot ulceration" OR "foot wound" OR "foot infection" OR Complication) AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxyvitamin D")
Google Scholar	All	allintitle: "Diabetic foot ulcer" "vitamin D"
		allintitle: Diabetes complication "vitamin D"
MedRvix, BioRvix	All	Full text or abstract or title "Diabetic foot ulcer vitamin D" (match whole all)
		Full text or abstract or title "Diabetes complication vitamin D" (match whole all)
Garuda	All	diabetes vitamin D