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The association between vitamin D receptor gene polymorphism FokI and type 2 diabetic kidney disease and its molecular mechanism: a case control study

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Abstract

Background The role of the vitamin D receptor single nucleotide polymorphism FOKI (VDR-FOKI) (rs2228570) in genetic susceptibility to type 2 diabetic kidney disease (T2DKD) remains uncertain. This study investigated the relationship between VDR-FOKI and T2DKD within the Chinese Plateau Han population and analyzed the underlying mechanisms.

Methods A total of 316 subjects were enrolled, including 44 healthy adults, 114 individuals with type 2 diabetes mellitus (T2DM), and 158 patients with T2DKD. According to the 2023 American Diabetes Association Diabetes Guidelines, patients with T2DKD were categorized into low-medium-risk and high-risk groups based on estimates of glomerular filtration rate and urinary albumin-to-creatinine ratio. The VDR-FokI genotypes of all participants were identified using the Taqman probe and classified as homozygous mutant genotypes (C/C or FF), heterozygous mutant genotypes (C/T or Ff), and homozygous wild genotypes (T/T or ff). Plasma levels of malondialdehyde (MDA), glutathione (GSH), and superoxide dismutase activity (SOD) were assessed in T2DKD patients with FF and ff genotypes. Additionally, the levels of plasma VDR, GPX4, and P53 were determined using ELISA, while the relative expressions of VDR mRNA, GPX4 mRNA, and TP53 mRNA in whole blood were measured by RT-qPCR.

Results The T2DM patients with the ff genotype exhibited a 2.93-fold increased likelihood of developing T2DKD compared to those with the FF genotype ($OR_{adjusted}$ = 2.93; 95% CI: 1.142–7.513). Additionally, they were 2.01 times more likely to develop T2DKD than individuals with the FF and Ff genotypes ($OR_{adjusted}$ = 2.01; 95% CI: 1.008–4.006). However, no significant differences in VDR-FokI genotype distribution were observed between the healthy control group and the T2DM group, as well as between the low-medium-risk and high-risk groups of T2DKD. Furthermore, T2DKD patients with the ff genotype had significantly higher plasma levels of MDA compared to those with the FF genotype. In contrast, plasma GSH and SOD content was significantly lower in the ff genotype patients ($P < 0.05$).

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Additionally, the GPX4 concentration in ff genotype patients was significantly lower than in FF genotype patients [14.88 (11.32,22.39) vs. 12.76 (8.55,13.75), $P=0.037$]. Nevertheless, no statistically significant difference was observed in the expression of VDRmRNA, GPX4mRNA, TP53mRNA, plasma VDR, and plasma P53.

Conclusions The ff genotype of VDR-FokI is a risk factor for T2DKD, and the potential mechanism may be related to ferroptosis. However, It is not associated with T2DM or the progression of T2DKD.

Keywords Vitamin D receptor, Single nucleotide polymorphism, Rs2228570, Type 2 diabetic kidney diseases, Ferroptosis

Background

Type 2 diabetic kidney disease (T2DKD) represents a manifestation of kidney damage induced by microangiopathy in type 2 diabetes mellitus (T2DM). It is the main cause of chronic and end-stage renal disease [1]. Notably, there is significant individual variability in susceptibility to T2DKD, with some individuals with type 2 diabetes developing T2DKD while others do not, even when they have similarly high blood glucose levels [2]. Therefore, individualized risk assessment and treatment are crucial for the prevention and treatment of T2DKD.

The vitamin D receptor (VDR) gene, located on the long arm of human chromosome 12 (12q13.11), consists of 9 exons and spans approximately 75 kb. It functions as a ligand-dependent nuclear transcription factor. A single nucleotide polymorphism, FokI, in the VDR gene, is caused by a T > C base change in the second exon, which is precisely where the start codon is located. This mutation results in a translation frameshift, leading to the synthesis of a truncated 424 amino acid protein (full-length 427aa) instead of the normal protein [3–5]. A recent study from the United Kingdom, which followed pre-diabetic patients ($n=56,387$) for 12 years, found that homozygous (C/C) individuals with the single nucleotide polymorphism FokI locus (rs2228570) of the VDR gene had a lower risk of vascular complications [6]. The association between VDR-FokI and T2DKD is evidently influenced by population-specific factors, leading to varying results across different populations [7, 8]. Significantly, research highlights disparities in the susceptibility to disease associated with VDR-FokI across diverse geographical regions [9]. Limited research has explored this correlation in Asian populations, particularly lacking in the context of high-altitude communities.

Ferroptosis, a distinct mode of programmed cell death dependent on iron, has garnered significant attention in recent years. Research has established the crucial role of ferroptosis in T2DKD [10, 11]. Bioinformatic analyses identified VDR and TP53 as factors associated with ferroptosis in diabetic nephropathy [12–15]. Furthermore, associations between VDR and TP53 have been observed in several tumor-related diseases [16, 17]. However, it remains unclear whether VDR and TP53 are connected to T2DKD through ferroptosis, particularly under the specific genetic context of the FOKI single nucleotide polymorphism in VDR.

To address this knowledge gap, our current investigation was carried out in Kunming, Yunnan Province (at an average altitude of approximately 2000 m), to explore the correlation between VDR-FokI and T2DKD. Additionally, we assessed the expression of VDRmRNA, GPX4mRNA, TP53mRNA, and their respective proteins in the blood of T2DKD patients with FF and ff genotypes of VDR-FokI to elucidate the potential mechanism underlying the association between VDR-FokI and T2DKD.

Methods

Study population selection

A total of 316 subjects were included in this study, consisting of 44 healthy adults, 114 patients with T2DM, and 158 patients with T2DKD, all participants were of Chinese Han ethnicity and had been long-term residents (≥5 years) in Kunming. Samples were obtained from patients visiting the First Affiliated Hospital of Kunming Medical University and healthy individuals undergoing physical examination at the health examination Center from January 2023 to December 2023. Inclusion criteria specified an age range of 18–70 years, a body mass index (BMI) between 18.5 and 28.0 kg/m^2, and a diagnosis of T2DKD or type 2 diabetes patients according to the 2023 edition of the American Diabetes Association "Diabetes Medical Standards" [18, 19]. Participants with other acute or chronic kidney diseases, acute complications of diabetes, urinary tract infection, urinary tract stones, infectious diseases, or pregnancy were excluded. Data collection was accomplished through face-to-face interviews conducted by the researchers and access to the medical record management system of the First Affiliated Hospital of Kunming Medical University (Supplementary File 1 for interview content). Written consent was obtained from all participants.

According to the 2023 edition of the ADA "Diabetes Medical Standards" [19], the combined estimates of glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio (UACR) categorized the risk of progression of T2DKD into two groups: low-medium-risk and high-risk groups. The criteria for the low-medium risk group are UACR between 30 and 300 mg/g and eGFR ≥ 60

mL/(min^{-1}×1.73m^2), while the high-risk group includes individuals with UACR between 30 and 300 mg/g and eGFR < 60 mL/(min^{-1}×1.73m^2), or UACR ≥ 300 mg/g.

Demographic, anthropometric and clinical data

Demographic and anthropometric information encompassed a range of variables, including age, sex, body mass index(BMI), duration of diabetes, history of hypertension, history of coronary heart disease, history of stroke, family history of diabetes, smoking history, use of sodium-glucose cotransporter 2 (SGLT2) inhibitors drugs, use of glucagon-like peptide 1 (GLP1) drugs, use of angiotensin receptor blocker (ARB) or angiotensin-converting-enzyme inhibitor (ACEI) drugs during disease, Additionally, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by an arm electronic sphygmomanometer after a resting period of half an hour on the day of admission.

The clinical test data comprised a comprehensive array of parameters, including white blood leukocyte count(WBC), neutrophil percentage (NEU%), neutrophil absolute value, lymphocyte absolute value, neutrophil-to-lymphocyte ratio (NLR), and fasting plasma glucose(FPG), glycosylated hemoglobin A1c (HbAlc), fasting insulin(FINS), fasting C-peptide(FCP) and 25 hydroxyvitamin D[25(OH)D], total cholesterol(TC), triglyceride(TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum albumin, serum calcium, serum uric acid(UA) and UACR. The specific detection methods employed were as follows: WBC, NEU%, neutrophil absolute value, and lymphocyte absolute value were determined by flow cytometry; FPG was measured by hexokinase; HbAlc was assayed via immunoassay; FPI, fasting C-peptide, and 25(OH)D were assayed by chemiluminescence; UA was assayed by uricase colorimetric assay; TC was assayed by cholesterol oxidase; TG was assayed by GPO-PAP; and HDL-C and LDL-C were assayed by surface-active agent clearance; serum calcium and urine albumin were assayed by colorimetric assay; And urinary creatinine was assayed by enzymatic assay. The estimated glomerular filtration rate (eGFR) was calculated by the simplified MDRD formula [eGFR = 186*Scr(mg/dl)-1.154* age-0.203 (mL/min/1.73m^2)] [20].

Sample collection and storage

Blood samples were collected from each healthy control individual, patient with type 2 diabetes, and patient with T2DKD. Approximately 5 mL of venous blood was drawn into an EDTA anticoagulant tube using a disposable blood collection needle, with all necessary sterile measures being taken. The EDTA tube was then allowed to stand at room temperature for a few minutes before being centrifuged at 3,000 rpm for 10 min. Subsequently, The plasma is then transferred with a micropipette. An appropriate volume of plasma was aliquoted into a cryopreservation tube. All samples (both plasma and whole blood) were stored at -80 ℃.

DNA extraction and VDR polymorphism FokI typing

The blood genomic DNA extraction kit (Tiangen Biotechnology Co., LTD.) was used for DNA extraction. The purity and concentration of the extracted DNA were assessed by a micro nucleic acid protein quantifier (Nano). DNA samples with a ratio of OD260/280 ranging from 1.7 to 1.9 were selected for amplification by the QuantStudio 6 Flex real-time fluorescence quantitative PCR. Genotyping was performed by the Thermo Field Taqman@SNP Genotyping Assays kit (Code: C_12060045_20, Thermo Fisher Scientific Inc.). The specific steps were as follows: 10 μl of Premix Ex Taq (Probe qPCR), 0.8 μl of Taqman@SNP Genotyping Assays, 0.2 μl of ROX Reference DyeII (50*), 20ng of DNA Template, and aseptic, enzyme-free water added to reach a final volume of 20 μl for solution matching. The reaction conditions were as follows: initial denaturation at 95℃ for 30 s, followed by 40 cycles of denaturation at 95℃ for 5 s, and annealing/extension at 60℃ for 30 s. Final analysis and automatic genotyping were performed by the Allelic Discrimination program. A subset of the genotyped DNA samples (six of each FF, Ff, and ff genotypes) was randomly selected for sequencing verification in Beijing Qingke Biotechnology Co., LTD.

Whole blood mRNA extraction and amplification

Whole blood mRNA was extracted by blood RNA extraction kit (Accurate Biology). The purity and concentration of DNA were detected by micro nucleic acid protein quantifier (Nano), and RNA samples with an OD260/280 ratio ranging from 1.8 to 2.0 were selected for reverse transcription by Bio PCR. Subsequently, real-time fluorescence quantitative PCR amplification was performed with QuantStudio 6 Flex real-time fluorescence quantitative PCR (RNA reverse transcription and amplification kits from Accurate Biology). Primers were designed by the primer designing tool available on the NCBI website, and their sequences are provided in Supplementary Table 1.

Enzyme-linked immunosorbent assay (ELISA)

VDR, GPX4, and P53 ELISA kit (Shanghai mlbio Co., LTD) were used to detect the plasma protein content. The sample and the ELISA Kit were equilibrated to room temperature before use and promptly utilized. 50ul of a standard product with different concentrations were added to the standard wells, 50ul of the sample was added to the sample wells, while the blank wells remained empty. Except for the blank wells, both the standard wells

and sample wells were supplemented with 100 µl of HRP-labeled test antibody, the plates were then sealed with a sealing plate membrane and incubated for 60 min in a light-free environment. Subsequently, the liquid in each well was discarded, and the wells were patted dry on absorbent paper. Pre-prepared washing liquid (350 µl) was added to each well, allowed to stand for 1 min, and then discarded. The wells were patted dry again on absorbent paper, and this washing step was repeated 5 times. Next, 50ul of substrate A and B liquid was added to each well, and the plate was placed in an incubator, protected from light, for 15 min. 50ul of stop solution was added to each well, and the OD value of each well was measured at a wavelength of 450 nm.

Determination of malondialdehyde (MDA), glutathione (GSH) and superoxide dismutase (SOD) levels

The levels of MDA, GSH and SOD in plasma were quantified using the respective detection kits provided by Solarbio: MDA content detection kit (BC0025), GSH content detection kit (BC1175), and SOD activity detection kit (BC5165). All assays were performed following the manufacturer's instructions, and sample concentrations were identified with a microplate reader at the corresponding wavelength (532 nm and 600 nm for MDA, 412 nm for GSH, and 450 nm for SOD).

Statistical analysis

Experimental data were expressed as mean ± SEM (Standard Error of Means) or median [inter-quartile range (IQR)]. Data analyses were carried out by the SPSS 25.0 (IBM, Inc., New York, NY, USA). Mapping was conducted by the GraphPad Prism (version 9.0) software. Logistic regression models were employed to estimate odds ratios (OR), a measure of relative risk, at 95% confidence intervals (95%CI). The statistical method conducted included the two-tailed student's t-test, Chi-square test, Fisher's exact test, and one-way ANOVA. Differences were considered significant at $P<0.05$. In conducting multiple comparisons, we utilized the Bonferroni method for *P*-value adjustment.

Results

Demographic, anthropometric and clinical data of the study subjects

The demographic, anthropometric, and clinical data are presented in Table 1. The mean ages of the healthy control group, T2DM group, and T2DKD group were 52.32 ± 6.85,57.48 ± 10.85 and 59.73 ± 12.17, respectively. The age of the healthy control group was significantly lower than that of the T2DM group and T2DKD group, but there were no significant differences in sex proportion and the distribution frequency of VDR-FokI genotypes among the three groups. TC, LDL-C, HDL-C, and VDR in the healthy control group were significantly higher than those in the T2DM group, and FPG was significantly lower than that in the T2DM group. There was no significant difference in serum creatinine, eGFR, serum uric acid, and TG between the healthy control group and the T2DM group (Table 1).

The duration of diabetes, the proportion of patients with hypertension, coronary heart disease, and diabetic retinopathy, as well as SBP, serum creatinine, UACR, TG, neutrophil percentage, NLR, HbA1C and FINS were significantly lower in the T2DM group compared to the T2DKD group. Conversely, eGFR, HDL-C, hemoglobin, serum albumin, and 25 (OH) D were significantly higher in the T2DM group. There were no statistically significant differences in age, sex, smoking status, history of stroke, atherosclerosis, family history of diabetes, use of SGLT2 inhibitors, GLP1 and ARB or ACEI drugs, DBP, TC, LDL-C, FPG, serum calcium or FCP between the T2DM group and the T2DKD group (Table 1).

Genotypic distribution of FokI (rs2228570) polymorphisms in healthy control group, T2DM group and T2DKD group

The *P* values of the Hardy-Weinberg genetic balance test in the healthy control group, T2DM group, and T2DKD group were greater than 0.05, indicating that the sample genotypes were evenly distributed within the population and in a state of genetic equilibrium, thus meeting the quality control criteria (Supplementary Table 2).

Logistic regression was employed to assess the association between the VDR-FokI genotype and T2DM, as well as with T2DKD, across various genetic models. No significant differences in genotype distribution were observed between the type 2 diabetes group and the healthy control group in the homozygotes (ff vs. FF), recessive model (ff vs. FF + Ff), and dominant model (Ff + ff vs. FF) (Table 2).

Furthermore, After adjusting for the duration of diabetes, hypertension history, HbA1c, serum uric acid, TC, TG, LDL-C and HDL-C, the T2DM patients with the ff genotype exhibited a 2.93-fold increased likelihood of developing T2DKD compared to those with the FF genotype ($OR_{adjusted}$ = 2.93; 95% CI: 1.142–7.513). Additionally, they were 2.01 times more likely to develop T2DKD than individuals with the FF and Ff genotypes ($OR_{adjusted}$ = 2.01; 95% CI: 1.008–4.006). (Table 2). Supplementary Tables 3 and 4 present the parameter estimates for all covariates included in the aforementioned logistic model.

Demographic, anthropometric, and clinical data in low-medium-risk group and high-risk group at risk for T2DKD progression

Demographic, anthropometric, and clinical data for the low-medium-risk and high-risk groups of T2DKD progression are presented in Table 3. Compared with the

Table 1 Demographic, anthropometric and clinical data of the study subjects

Observational index	Healthy control group($n=44$)	Type 2 diabetes group($n=114$)	Type 2 diabetic kidney disease group($n=158$)	X^2/H/F/Z/t value	*P* value
Male, *n*(%)	25 (56.82%)	73 (64.04%)	101 (63.92%)	0.831	0.660
Age, years	52.32 ± 6.85	57.48 ± 10.85[a]	59.73 ± 12.17[a]	20.306	**<0.001***
Serum creatinine, μmol/L	72.97 ± 12.57	71.38 ± 16.58	88.18 ± 40.83[ab]	15.494	**<0.001***
eGFR, mL/(min*1.73m^2)	93.81 ± 11.40	99.78 ± 22.26	87.69 ± 47.68[ab]	21.494	**<0.001***
Serum uric acid, μmol/L	327.36 ± 88.74	348.90 ± 93.69	369.64 ± 97.48[a]	3.937	**0.020***
TC, mmol/L	5.09 ± 0.95	4.31 ± 1.09[a]	4.35 ± 1.20[a]	8.611	**<0.001***
TG, mmol/L	1.64 (1.20, 1.96)	1.45 (0.98, 2.12)	1.63 (1.20, 2.69)[b]	8.123	**0.017***
LDL-C, mmol/L	3.14 ± 0.86	2.61 ± 0.98[a]	2.51 ± 1.07[a]	6.860	**0.001***
HDL-C, mmol/L	1.31 ± 0.27	1.10 ± 0.32[a]	0.97 ± 0.33[ab]	21.864	**<0.001***
FPG, mmol/L	4.77 ± 0.32	6.67 ± 2.57[a]	7.28 ± 3.63[a]	28.677	**<0.001***
VDR, ng/L	3.92 (2.38, 5.87)	0.45 (0.32, 0.91)[a]	0.76 (0.25, 1.53)[a]	72.659	**<0.001***
Diabetes duration, years	-	10.00 (2.00, 13.25)	13.00 (5.75, 18.00)	−3.805	**<0.001***
Smoking history, *n*(%)	-	34 (29.82%)	52 (32.91%)	0.292	0.589
History of hypertension, *n*(%)	-	50 (43.86%)	92 (58.23%)[b]	5.479	**0.019***
history of coronary heart disease, *n*(%)	-	7 (6.14%)	23 (14.56%)[b]	4.780	**0.029***
history of stroke, *n*(%)	-	5 (4.39%)	17 (10.76%)	3.618	0.057
History of atherosclerosis, *n*(%)	-	71 (62.28%)	99 (62.66%)	0.004	0.949
Family history of diabetes, *n*(%)	-	22 (19.30%)	29 (18.35%)	0.039	0.844
History of diabetic retinopathy, *n*(%)	-	5 (4.39%)	32 (20.25%)[b]	14.186	**<0.001***
History of SGLT2 inhibitor use, *n*(%)	-	25 (21.93%)	30 (18.99%)	0.355	0.551
History of GLP1 drug use, *n*(%)	-	5 (4.39%)	9 (5.70%)	0.233	0.629
History of use of ARBs or ACEIs, *n*(%)	-	29 (25.44%)	47 (29.75%)	0.610	0.435
SBP, mmHg	-	118.31 ± 19.87	127.13 ± 23.08[b]	−3.374	**0.001***
DBP, mmHg	-	77.59 ± 10.06	79.08 ± 12.62	−1.081	0.281
UACR, mg/g	-	6.84 (4.41, 13.85)	110.89 (53.44, 370.06)[b]	−14.033	**<0.001***
Hemoglobin, g/L	-	150.33 ± 13.87	142.39 ± 21.11[b]	267.845	**<0.001***
Neutrophil percentage, %	-	57.00 ± 10.70	61.46 ± 10.78[b]	−3.386	**0.001***
NLR	-	1.68 (1.26, 2.40)	1.93 (1.48, 2.90)[b]	−2.399	**0.016***
Serum albumin, g/L	-	43.23 ± 3.72	40.06 ± 5.03[b]	5.968	**<0.001***
25 (OH) D, nmol/L	-	60.58 ± 28.20	53.25 ± 22.82[b]	2.323	**0.021***
Serum calcium, mmol/L	-	2.31 ± 0.11	2.32 ± 0.15	−0.730	0.466
HbA1c, %	-	8.58 ± 1.95	9.38 ± 2.17[b]	−3.100	**0.002***
FINS, mU/L	-	10.58 (5.78, 16.05)	15.54 (9.00, 27.99)[b]	−3.865	**<0.001***
FCP, ng/mL	-	1.33 (0.81, 1.97)	1.45 (0.74, 2.20)	−0.513	0.608
VDR-FokI genotype				7.530	0.110
FF	13 (29.55%)	35 (30.70%)	40 (25.32%)		
Ff	28 (63.64%)	61 (53.51%)	81 (51.27%)		
ff	3 (6.82%)	18 (15.79%)	37 (23.42%)		

[a]Compared with the healthy control group *P* value <0.017; [b]Compared with the T2DM group *P* value <0.017;; *$P<0.05$;-: This indicator was not detected in the healthy group

SBP, systolic blood pressure; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *UACR*, urinary albumin-to-creatinine ratio; *NLR*, neutrophil-lymphocyte ratio; *TC*, total cholesterol; *TG*, triglyceride; *LDL-C*, low-density lipoprotein cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *25 (OH)D*, 25-hydroxyvitamin D; *HbA1c*, hemoglobin A1c; *FPG*, fasting plasma glucose; *FINS*, fasting insulin; *FCP*, Fasting C-peptide

low-medium-risk group, the high-risk group exhibited significantly elevated levels of hypertension incidence, stroke incidence, serum creatinine, UACR, NLR, and serum uric acid. In contrast, eGFR and 25(OH)D levels were notably decreased. There were no significant differences in other parameters, including the distribution frequency of VDR-FokI genotypes, between the two groups.

Furthermore, considering the influence of sex on serum creatinine and eGFR, we stratified serum creatinine and eGFR by sex, with 55 men and 39 women in the low-to-medium risk group and 46 men and 18 women in the high-risk group. The results indicated that serum creatinine levels in both men and women within the high-risk group were significantly elevated compared to those in the low-to-medium risk group. In contrast, the eGFR in men from the high-risk group was significantly lower. However, no statistically significant differences in eGFR

Table 2 Comparison of VDR-FokI genotype distribution under different genetic models

		Homozygotes		Invisible model		Dominant model	
		OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Healthy control group vs. T2DM group	Model 1	2.229(0.562–8.842)	0.254	2.562(0.715–9.178)	0.148	0.947(0.443–2.024)	0.887
	Model 2	4.821 (0.579–40.128)	0.146	3.540 (0.765–8.136)	0.095	1.240 (0.467–3.290)	0.666
T2DM vs. T2DKDgroup	Model 1	1.799(0.873–3.707)	0.112	1.631(0.874–3.043)	0.124	1.307(0.765–2.233)	0.327
	Model 3	**2.930 (1.142–7.513)**	**0.025**	**2.009 (1.008–4.006)**	**0.048**	1.404 (0.769–2.565)	0.269

Model 1: Univariate logistic regression analysis

Model2: Adjusted for age, serum uric acid, TC, TG, LDL-C, HDL-C, FPG

Model 3: Adjusted for diabetes course, hypertension history, HbA1c, serum uric acid, TC, TG, LDL-C and HDL-C

Homozygotes: T/T vs. C/C (ff vs. FF); Invisible model; T/T vs. C/C+C/T (ff vs. FF+Ff): Dominant model; C/T+T/T vs. C/C (Ff+ff vs. FF)

were observed in women between the low-to-medium risk group and the high-risk group. (Table 3).

FokI genotype distribution in low-medium-risk group and high-risk group for T2DKD progression under different genetic models

Under various genetic models, no significant differences were observed in the distribution of VDR-FokI genotypes between the low-medium-risk group and high- risk group. Additionally, after adjusting for hypertension history, HBA1c, TC, TG, LDL-C, HDL-C, blood uric acid, NLR, and serum albumin, the distribution of VDR-FokI genotypes remained statistically insignificant between the two groups (Table 4). Supplementary Table 5 present the parameter estimates for all covariates included in the aforementioned logistic model.

Demographic, clinical and experimental data of T2DKD patients in FF genotype group and ff genotype group

Among T2DKD patients, we identified 37 patients with FF genotype and 36 with ff genotype. Notably, the duration of diabetes was significantly shorter in patients with the ff genotype compared to those with the FF genotype [15.00 (7.50, 20.00) vs. 11.00 (5.00, 14.00), $P=0.039$]. However, there were no significant differences in other demographic and clinical data between the two groups (Supplementary Table 6).

Furthermore, to investigate the potential mechanisms underlying the differences in T2DKD susceptibility associated with distinct genotypes of VDR-FOkI, we compared blood markers of oxidative stress and the expression levels of VDR, GPX4, and P53 in homozygous FF and ff patients. The results indicated that patients with the ff genotype had significantly higher plasma levels of MDA compared to those with the FF genotype, while plasma GSH and SOD content was significantly lower in the ff genotype patients ($P<0.05$) (Supplementary Tables 3 and Fig. 1A-C). The GPX4 concentration in ff genotype patients was significantly lower than in FF genotype patients [14.88 (11.32,22.39) vs. 12.76 (8.55,13.75), $P=0.037$). However, no statistically significant differences were detected in the plasma levels of VDR and P53, nor the expression of VDRmRNA, GPX4mRNA, and TP53mRNA in whole blood between the two genotype groups(Supplementary Tables 3 and Fig. 1D **and E**).

Discussion

T2DKD has long been recognized as a clinical challenge attributed to its intricate pathogenesis and unfavorable prognosis. Identification of predisposing risks and elucidation of the underlying mechanisms are crucial for prevention and management. Our study indicates that a particular single nucleotide polymorphism (SNP) in the VDR gene, FokI, is linked to T2DKD in the Chinese Han population. The potential mechanism behind this association may involve ferroptosis. Nevertheless, this SNP is not correlated with T2DM or the progression of T2DKD.

Observational studies have revealed a higher prevalence of vitamin D deficiency among patients with T2DKD [21–23]. However, many studies have failed to fully account for geographical variables, such as altitude, and their effect on vitamin D production. To address this knowledge gap, our study was conducted in Kunming, Yunnan Province, China, situated at an average altitude of approximately 2000 m, where intense ultraviolet radiation facilitates vitamin D synthesis. Despite the high-altitude setting, we discovered similar trends and noted a progressive decline in serum 25(OH)D levels with advancing stages of T2DKD. Hence, it is crucial to consider the impact of vitamin D on T2DKD even in environments with elevated altitudes and ample ultraviolet exposure.

The biological effects of vitamin D rely on its binding to the VDR. Mutations in the VDR gene can modify the response of various tissues to vitamin D [24]. Among the single nucleotide polymorphism (SNP) of the VDR gene, FokI (rs2228570) has garnered significant attention as it is the sole variant altering the VDR protein structure and is not in linkage disequilibrium with other VDR gene SNP [3, 25]. Previous investigations in Asian and South American populations have shown that the ff genotype of VDR-FokI poses a risk for T2DM [26–29]. Yet, no such relationship was observed in a study conducted within the United Arab Emirates population [30]. In our study,

Table 3 Demographic, anthropometric, and clinical data in low-medium risk group and high risk group at risk for T2DKD progression

Observational index	Low-to-medium risk group (*n* = 94)	High-risk group(*n* = 64)	X^2/t/z	*P* value
Male, *n*(%)	55 (58.51%)	46(71.88%)	2.949	0.086
Age, years	60.23 ± 12.01	59.00 ± 12.45	0.625	0.533
BMI, kg/m^2	24.07 ± 4.19	24.80 ± 3.28	−1.173	0.243
Diabetes duration, years	12.00 (5.00, 8.00)	13.50 (7.00, 20.00)	−0.963	0.336
Smoking history, *n*(%)	29(30.85%)	23(35.94%)	0.446	0.504
History of hypertension, *n*(%)	48(51.06%)	44(68.75%)	4.897	**0.027***
history of coronary heart disease, *n*(%)	11(11.70%)	12(18.75%)	1.521	0.218
history of stroke, *n*(%)	5(5.32%)	12(18.75%)	7.153	**0.007***
History of atherosclerosis, *n*(%)	54(57.45%)	45(70.31%)	2.694	0.101
Family history of diabetes, *n*(%)	19(20.21%)	10(15.63%)	0.535	0.465
History of diabetic retinopathy, *n*(%)	16(17.02%)	16(25.00%)	1.501	0.221
History of SGLT2 inhibitor use, *n*(%)	16(17.02%)	14(21.88%)	0.583	0.445
History of GLP1 drug use, *n*(%)	7(7.45%)	2(3.13%)	0.642	0.423
History of use of ARBs or ACEIs, *n*(%)	23(24.47%)	24(37.50%)	3.094	0.079
SBP, mmHg	127.22 ± 24.46	126.98 ± 21.09	0.064	0.949
DBP, mmHg	79.40 ± 11.36	78.59 ± 14.36	0.378	0.706
Serum creatinine, μmol/L	72.20 ± 15.50	111.66 ± 53.47	−5.741	**<0.001***
Serum creatinine for males, μmol/L	79.41 ± 13.83	117.56 ± 54.37	−4.636	**<0.001***
Serum creatinine for females, μmol/L	62.04 ± 11.62	96.57 ± 49.34	−2.932	**0.009***
eGFR, mL/(min*1.73m^2)	95.49 ± 21.60	76.23 ± 68.94	2.164	**0.034***
eGFR for males, mL/(min*1.73m^2)	95.54 ± 18.45	70.31 ± 26.47	5.451	**<0.001***
eGFR for females, mL/(min*1.73m^2)	95.43 ± 25.66	91.35 ± 124.18	0.138	**0.892**
UACR, mg/g	61.39 (41.56, 109.57)	543.08 (309.1176.35)	−9.043	**<0.001***
Hemoglobin, g/L	144.89 ± 20.84	138.72 ± 22.19	1.818	0.071
Neutrophil percentage, %	59.94 ± 10.71	63.71 ± 10.55	−2.188	**0.030***
Neutrophil absolute value	4.32 ± 3.43	4.95 ± 2.52	−1.260	0.210
Lymphocyte absolute value	2.05 ± 0.64	1.90 ± 0.75	1.323	0.188
NLR	1.74 (1.33, 2.30)	2.21 (1.84, 3.70)	−3.781	**<0.001***
Plasma fibrinogen, g/L	4.03 ± 1.53	4.38 ± 1.32	−1.317	0.190
Serum albumin, g/L	41.05 ± 4.88	38.60 ± 4.93	3.094	**0.002***
Serum uric acid, μmol/L	344.89 ± 89.87	406.00 ± 97.49	−4.054	**<0.001***
TC, mmol/L	4.24 ± 1.09	4.51 ± 1.34	−1.373	0.172
TG, mmol/L	1.55 (1.19, 2.44)	1.82 (1.26, 3.13)	−1.548	0.122
LDL-C, mmol/L	2.51 ± 0.92	2.50 ± 1.27	0.005	0.996
HDL-C, mmol/L	0.96 ± 0.25	0.99 ± 0.42	−0.518	0.605
25 (OH) D, nmol/L	57.97 ± 23.90	46.01 ± 19.07	3.258	**0.001***
VDR, ng/mL	0.67 (0.22, 1.44)	0.80 (0.27, 1.73)	−1.445	0.148
HbA1c, %	9.59 ± 2.22	9.06 ± 2.06	1.517	0.131
FPG, mmol/L	7.40 ± 3.16	7.12 ± 4.25	0.458	0.648
FINS, mU/L	15.62 (9.03, 27.71)	15.37 (8.92, 29.05)	−0.239	0.811
FCP, ng/mL	1.42 (0.74, 2.14)	1.54 (0.63, 2.42)	−0.470	0.638
VDR-FokI genotype			1.114	0.573
FF	25 (26.60%)	15 (23.44%)		
Ff	45 (47.87%)	36 (56.25%)		
ff	24 (25.53%)	13 (20.31%)		

**P*<0.05

SBP, systolic blood pressure; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *UACR*, urinary albumin-to-creatinine ratio; *NLR*, neutrophil-lymphocyte ratio; *TC*, total cholesterol; *TG*, triglyceride; *LDL-C*, low-density lipoprotein cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *25 (OH)D*, 25-hydroxyvitamin D; *HbA1c*, hemoglobin A1c; *FPG*, fasting plasma glucose; *FINS*, fasting insulin; *FCP*, Fasting C-peptide

we did not discover an association between VDR-FokI and T2DM. This disparity may be influenced by regional, population-specific, and altitude-related factors, emphasizing the necessity for further cohort studies to validate these observations. Notably, we observed that individuals with T2DM having the ff genotype of VDR-FokI exhibited an increased likelihood of developing T2DKD compared to those with the FF genotype ($OR_{adjusted}$ = 2.930;

Table 4 FokI genotype distribution in low-medium group and high risk group for T2DKD progression under different genetic models

		Homozygotes		Invisible model		Dominant model	
		OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Low-to-medium risk group vs. high-risk group	Model 1	0.903(0.356–2.289)	0.829	0.743(0.346–1.598)	0.448	1.184(0.566–2.474)	0.654
	Model 2	2.068(0.537–7.968)	0.291	1.256(0.505–3.120)	0.624	1.413 (0.574–3.479)	0.452

Model 1: Univariate logistic regression analysis

Model2: Adjusted for diabetes course, hypertension history, HBA1c, TC, TG, LDL-C, HDL-C, serum uric acid, NLR, and serum albumin

Homozygotes: T/T vs. C/C (ff vs. FF); Invisible model; T/T vs. C/C+C/T (ff vs. FF+Ff): Dominant model; C/T+T/T vs. C/C (Ff+ff vs. FF)

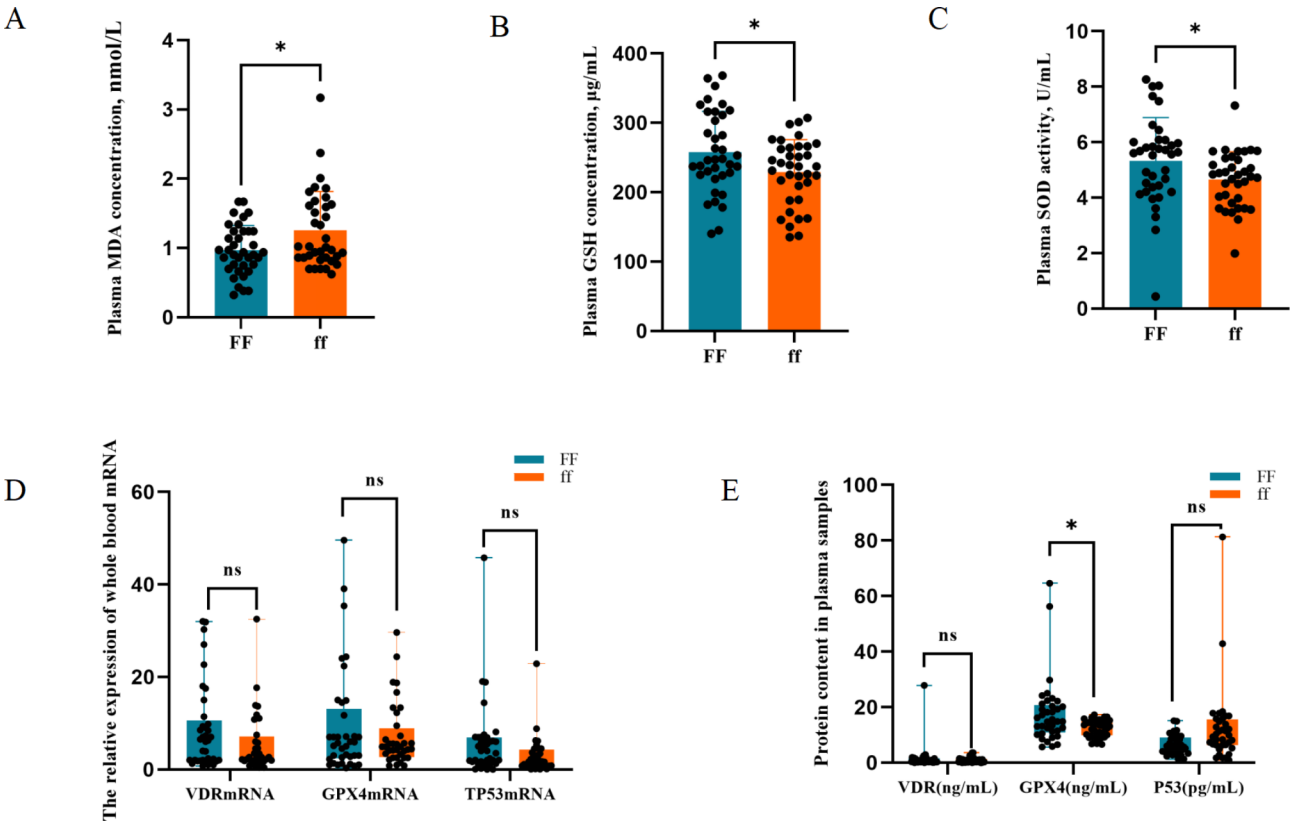

Fig. 1 The oxidative stress markers MDA (**A**), GSH (**B**) and SOD (**C**), as well as the expression levels of VDR, GPX4, and TP53 mRNA (**D**) and protein (E) in the blood of T2DKD patients with FF genotype and ff genotype. * $P<0.05$; ns indicates no significance

95% CI: 1.142–7.513) and FF+Ff genotype individuals ($OR_{adjusted}$ = 2.009; 95% CI: 1.008–4.006). Our findings align with a recent prospective cohort study [6] and have also been replicated in Caucasian populations [7, 31, 32]. However, a recent meta-analysis did not establish an association between VDR-FokI and T2DKD in Asian populations due to the limited inclusion of Asian studies [8]. Hence, we propose that forthcoming studies should include a more comprehensive array of samples from diverse Asian populations to confirm these outcomes.

Once T2DKD initiates adverse pathophysiological changes, reversing them becomes exceedingly challenging [33]. Early identification of risks can aid in designing treatment strategies and mitigating adverse renal outcomes in diabetic nephropathy patients. Our study suggests that a history of hypertension, percentage of neutrophils, NLR, uric acid levels, serum albumin levels, and serum 25(OH)D concentration could be potential risk factors for T2DKD progression, while VDR-FokI does not appear to be associated with T2DKD progression. Researchers have recently developed a weighted risk model for assessing the progression from diabetic nephropathy to chronic kidney disease, which aligns with the risk factors identified in our study [34]. However, this model overlooks serum 25(OH)D levels and hypertension history. We propose establishing similar models or conducting prospective studies that include these risk factors to more comprehensively evaluate the residual risk of diabetic nephropathy progression.

The pathogenesis of T2DKD remains incompletely understood. However, sustained hyperglycemia leads to the formation of advanced glycosylation end products,

cytokines, growth factors, and inflammatory mediators, disrupting the homeostasis of the internal environment and initiating oxidative stress, endoplasmic reticulum stress, inflammation, and mitochondrial dysfunction. Ultimately, these processes culminate in various forms of regulated cell death, representing the primary pathogenic mechanisms of T2DKD [35]. In recent years, ferroptosis has garnered significant attention as a unique iron-dependent form of programmed cell death, different from apoptosis, necroptosis, and pyroptosis. Clinical trials, as well as cell and animal models, have established the involvement of ferroptosis in the pathogenesis of T2DKD [10, 11]. VDR activation effectively mitigates renal damage in diabetic nephropathy. Bioinformatics analyses have identified VDR as a transcription factor associated with ferroptosis in diabetic nephropathy, and cellular and animal studies indicate that VDR activation can ameliorate renal injury in diabetic nephropathy by targeting ferroptosis [12–14]. However, the association between the FokI polymorphism of the VDR gene and ferroptosis has not been previously reported. Our study revealed that, compared to T2DKD patients with the FF genotype, those with the ff genotype exhibited significantly elevated plasma levels of the oxidative stress marker MDA. Conversely, levels of the antioxidant factors GSH and SOD were significantly reduced, along with plasma levels of GPX4 in T2DKD patients with the ff genotype when compared to their FF genotype counterparts. These findings suggest a potential mechanism wherein variations in the incidence of T2DKD may be associated with distinct genetic patterns of the VDR-FokI polymorphism, which could be linked to ferroptosis. Furthermore, we investigated the plasma levels of P53 and TP53 mRNA expression in patients to explore potential signaling pathways. P53, a tumor-suppressor gene activated by various stress stimuli, acts as a transcription inhibitor of SLC7A11, blocking cysteine intake and promoting ferroptosis. Bioinformatics analysis identifies TP53 as a primary diagnostic marker for ferroptosis in diabetic nephropathy [15, 36, 37]. However, in our study, we did not find a statistical difference in TP53 expression in the blood of T2DKD patients with FF and ff genotypes. Although we observed a decreasing trend in TP53 mRNA expression in FF genotype patients, plasma P53 protein expression showed an increasing trend. This discrepancy may be attributed to the relatively small sample size (37 patients with FF genotype, 36 patients with ff genotype) and the influence of various factors on human blood components.

Research indicates that the transcriptional activity of the truncated VDR protein (424aa) is higher in individuals with the VDR-FokI FF genotype compared to those with the full-length protein (427aa) in VDR-FokI ff genotype individuals [24]. However, our current study did not uncover significant differences in VDR mRNA and protein expression between T2DKD patients with the FF and ff genotypes. This finding aligns with previous studies in periodontitis patients, which also did not observe such differences. Notably, these researchers discovered that treatment with 1,25(OH)2D3 in human gingival fibroblasts and periodontal ligament cells resulted in alterations in the transcription of RANKL/OPG genes, which are regulated by VDR, impacting disease progression [38, 39]. VDR-FokI may elicit physiological effects by modulating the expression of other genes, underscoring the importance of further in vivo and in vitro investigations to validate these associations in diverse disease contexts.

Our study has various advantages. Firstly, we assessed the impact of VDR-FokI on the development of T2DKD in a Han population residing in highland areas of China. To the best of our knowledge, such studies are scarce in Asian populations, particularly regarding the influence of VDR-FokI on the progression risk of T2DKD. Secondly, the use of samples from a representative random sample of the permanent population, chosen based on strict inclusion criteria, enhances the robustness of our study. Thirdly, our discovery that the potential mechanism through which VDR-FokI influences susceptibility to T2DKD could be linked to ferroptosis is, as far as we are aware, the first exploration of the pathogenesis of T2DKD in relation to VDR-FokI. In conclusion, this study offers insights into the susceptibility of T2DKD and potential mechanisms in the Han population of China's highland regions in terms of VDR-FokI. However, there are limitations to our study. Firstly, we limited our evaluation to the relationship between the VDR gene FokI polymorphism and T2DKD in the Han population of China's highland regions, potentially failing to fully account for the genetic diversity of VDR. Future research should consider investigating additional VDR gene polymorphisms like BsmI, ApaI, and TaqI, which could also be informative in these processes. Secondly, our exploration of the susceptibility mechanism using blood samples from T2DKD patients may not accurately reflect the true situation due to the complexity of human blood composition and its susceptibility to various influences. Finally, the relatively small sample size and the observational nature of our study mean that residual confounding factors cannot be entirely eliminated. Therefore, extensive investigations involving larger sample sizes and supplemental in vitro and in vivo experiments are crucial.

Conclusions

In summary, our study has established a significant association between VDR-FokI and T2DKD in the Han population residing in the plateau regions of China. However, it does not demonstrate any associations with T2DM or the progression of T2DKD. We propose integrating

VDR-FokI into a precise medical prediction model to assess the susceptibility of T2DKD. Furthermore, it is imperative to delve into the potential mechanism linking VDR-FokI and ferroptosis via in vitro and in vivo experiments to establish a foundation for devising targeted prevention and treatment strategies for individuals with the ff genotype.

Abbreviations

VDR-FokI	The single nucleotide polymorphism FokI of the VDR gene
T2DKD	Type 2 diabetic kidney disease
T2DM	Type 2 diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
RT-qPCR	Real-time polymerase chain reaction
VDR	Vitamin D receptor
GPX4	Glutathione peroxidase 4
eGFR	Estimates of glomerular filtration rate
UACR	Urinary albumin to creatinine ratio
BMI	Body mass index
SGLT2	Sodium-glucose cotransporter 2
GLP1	Glucagon-like peptide 1
ARB	Angiotensin receptor blocker
ACEI	Angiotensin-converting-enzyme inhibitor
OR	Odds ratios
95%CI	95% confidence intervals
SNP	Single nucleotide polymorphism
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
WBC	White blood leukocyte count
NEU%	Neutrophil percentage
NLR	Neutrophil-to-lymphocyte ratio
FPG	Fasting plasma glucose
HbAlc	Glycosylated hemoglobin A1c
FINS	Fasting insulin
FCP	Fasting C-peptide
TC	Total cholesterol
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
UA	Uric acid
MDA	Malondialdehyde
GSH	Glutathione
SOD	Superoxide dismutase

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

R. H., Y. Z. and Z. L. designed the research, collected, and analyzed data, and wrote the paper. S. F., R. Y., Z. R., R. Z., L. M., Z. W.and L. C. contributed to data acquisition. R.H., Y. Z. and Z. L. revised the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Review Committee of the First Affiliated Hospital of Kunming Medical University [(2023) Ethical Review L No. 30]. Informed consent was obtained from all patients for our research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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