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Original

Association of vitamin D status and genetic variants with type 2 diabetes in a Costa Rican population

(Asociación entre el estado de vitamina D y variantes genéticas con la diabetes tipo 2 en una población costarricense)

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ABSTRACT

Aim: To assess the association between plasma 25-hydroxyvitamin D levels, gene polymorphisms involved in vitamin D metabolism, and the risk of type 2 diabetes in a Costa Rican population. **Methods:** 578 adults were enrolled in a case-control study from an urban Costa Rican population. Blood samples were collected to measure circulating vitamin D levels, glucose, hemoglobin A1c, lipid profile, and for the genotyping of 14 vitamin D related SNPs. The associations between plasma 25-hydroxyvitamin D levels, clinical and biochemical variables, gene polymorphisms, and type 2 diabetes were tested. **Results:** Classical risks factors as body mass index (OR: 1.13, p <0.001), and arterial hypertension (OR: 3.31, p <0.001) were associated with type 2 diabetes. In addition, type 2 diabetes was associated with 25-hydroxyvitamin D levels (OR: 0.97, p = 0.023). Polymorphisms in the *GC* gene (rs4588, rs7041, rs3755967, and rs22522679) were associated with plasma levels of vitamin D (all-p values <0.036). None of the SNPs assessed were associated with type 2 diabetes. **Conclusion:** Our findings suggest that *GC* gene polymorphisms contribute to interindividual variability in vitamin D status. Although these variants were not directly associated with type 2 diabetes in the present study, their potential role in vitamin D–related metabolic pathways warrant further investigation.

Keywords: Diabetes mellitus, type 2; 25-hydroxyvitamin D; SNPs; obesity; genetic association studies.

RESUMEN

Objetivo: Analizar la asociación entre los niveles plasmáticos de 25-hidroxivitamina D, polimorfismos genéticos involucrados en el metabolismo de la vitamina D y el riesgo de diabetes tipo 2 en una población costarricense. **Métodos**: Se incluyeron 578 adultos en un estudio de casos y controles en una población urbana costarricense. Se recolectaron muestras de sangre para medir los niveles circulantes de vitamina D, glucosa, hemoglobina A1c, perfil lipídico y para el genotipado de 14 SNPs relacionados con la vitamina D. Se evaluaron las asociaciones entre los niveles plasmáticos de 25-hidroxivitamina D, las variables clínicas y bioquímicas, los polimorfismos genéticos y la diabetes tipo 2. **Resultados**: Los factores de riesgo clásicos como el índice de masa corporal (OR: 1.13, p <0.001) y la hipertensión arterial (OR: 3.31, p <0.001) se asociaron significativamente con la diabetes tipo 2. Además, la diabetes tipo 2 se asoció con los niveles plasmáticos de 25-hidroxivitamina D (OR: 0.97, p = 0.023); y polimorfismos en el gen *GC* (rs4588, rs7041, rs3755967 y rs22522679) se asociaron significativamente con los niveles plasmáticos de vitamina D (valores de p <0.036). Ninguno de los SNPs evaluados se asoció con la diabetes tipo 2. **Conclusión**: Nuestros resultados sugieren que polimorfismos en el gen *GC* contribuyen a la variabilidad interindividual en los niveles

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Abreviaturas:
25(OH)D; 25-hydroxyvitamin D
AHT; Arterial hypertension
BMI; Body mass index
BP; Blood pressure
DM2; Diabetes Mellitus type 2
FPG; Fasting plasma glucose
HbA1c; Hemoglobin A1c
HDL; High-density lipoprotein cholesterol
LDL; Low-density lipoprotein cholesterol
SNPS; Single nucleotide polymorphism
TC; Total cholesterol
TG; Triglycerides

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de vitamina D. Aunque estas variantes no se asociaron directamente con la diabetes tipo 2 en el presente estudio, su potencial implicación en las vías metabólicas relacionadas con la vitamina D requiere estudios adicionales.

Descriptores: Diabetes mellitus tipo 2, 25-hidroxivitamina D, SNPs, obesidad, estudios de asociación genética.

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Vitamin D is a hormone with pleiotropic effects, including the regulation of calcium, phosphorus, and bone homeostasis. Beyond these actions, vitamin D contributes to antioxidant activity, lipid and carbohydrate metabolism, immune system modulation, neural development, and plays a role in cancer prevention.[1,2] A biomarker for assessing vitamin D status is 25-hydroxyvitamin D (25(OH)D). The plasma level of 25(OH)D has emerged as an important modifiable risk factor for many diseases, including type 2 diabetes (DM2).

Genetic variants such as single nucleotide polymorphisms (SNPs) in genes involved in vitamin D biosynthesis, transport or function can affect circulating levels of this hormone. Some of these variants correspond to SNPs in the following genes: 7-dehydrocholesterol reductase (*DHCR7*)/NAD synthetase 1 (*NADSYN1*), vitamin D 25-hydroxylase (*CYP2R1*), vitamin D-1α-hydroxylase (*CYP27B1*), vitamin D-binding protein (*DBP* or *GC*), and vitamin D 24-hydroxylase (*CYP24A1*), among others.[3–6]

The link between vitamin D and DM2 was initially established through epidemiological observations showing that individuals with 25(OH)D deficiency had a higher risk of developing DM2.[7,8] However, studies conducted across different populations of Caucasian, Hispanic, and Asian origin have shown inconsistent results.[7–10] The effectiveness of long-term oral vitamin D supplementation in improving the metabolic profile remains controversial, as most clinical trials have failed to show that supplementation prevents the progression of prediabetic individuals to DM2.[11–13] Despite these findings, experimental evidence has supported the epidemiological associations and has proposed cellular mechanisms by which vitamin D deficiency may promote the onset of DM2.[2,14,15]

Latin American countries report alarming increases in obesity rates among both adults and children, which are related to the rising prevalence of chronic non-communicable diseases such as DM2.[16] In Costa Rica, the prevalence of DM2 is 14.8%, according to data from a national survey.[17] Characterization studies have examined both urban and rural populations in Costa Rica, focusing on the classic risk factors associated with the development of metabolic diseases. [18–20] While a low intake of vitamin D has been reported in a healthy urban sample, [21] there is a lack of information regarding circulating vitamin D levels in patients with DM2.

Given the current public health scenario and the limited information on vitamin D status in the Costa Rican population, particularly its association with DM2, this research aimed to fill this gap. The objective of this study was to analyze the association between plasma 25(OH)D levels, clinical variables, SNPs in genes involved in vitamin D metabolism, and the risk of developing DM2 in an urban Costa Rican population.

Methods

The present research followed a case-control study design and included a total of 578 subjects (262 controls and 316 cases). Participants were enrolled between 2011 – 2015 at Marcial Fallas Clinic, Desamparados, Costa Rica, a clinic that is part of the primary care level of the National Health Social Security System. Participants were ⩾ 20 years old and had at least two relatives from two previous generations born in the Costa Rican Central Valley. Cases included all participants with an established DM2 diagnosis according to the criteria defined by the American Diabetes Association.[22] The inclusion criteria for the control group were as follows: not being recognized as a DM2 patient according to self-report and verified in the clinical record, fasting plasma glucose (FPG) < 100 mg/dL, and no family history of DM2 in first-degree relatives. Exclusion criteria for controls were a personal history of gestational diabetes and prior or current treatment with hypoglycemic drugs. This study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Ethics Committee of the University of Costa Rica (VI-6467-2017).

Anthropometric and clinical measurements: Information on body weight, height, blood pressure (BP), and diagnosis of arterial hypertension (AHT) was obtained from the participants' clinical records and recorded by medical staff. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and participants were classified as having normal weight, overweight, or obese according to the criteria set by the WHO.[23]

The control group was classified as non-DM2. The non-DM2 group included participants with normal hemoglobin A1c (HbA1c) levels (<5.7%) and altered HbA1c levels (5.7% to <6.5%). To further categorized glycemic status, participants from the non-DM2 group with HbA1c <5.7% were classified as normal, while those with HbA1c levels between 5.7% to <6.5% were classified as prediabetic.

Biochemical measurements: Fasting blood samples were collected for the quantification of FPG, HbA1c, and lipid profile including total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides (TG) by standard laboratory methods with fresh plasma samples.

Plasma 25(OH)D concentration was determined by the Architect Immunoassay Method (Abbott Laboratories, IL, USA), using stored plasma samples at -80°C. Vitamin D status was categorized according to The Endocrine Society's Clinical Guidelines, with deficiency defined as 25(OH) D levels <20 ng/mL, insufficiency as levels between 20 and ⩽30 ng/mL, and sufficiency as levels ⩾30 ng/mL.[24]

SNPs selection and genotyping: We selected SNPs that have been previously associated with 25(OH) D levels or metabolic health outcomes in studies with Caucasian or Amerindian ancestry population, such as Insulin Resistance Atherosclerosis (IRAS) Family Study[6,25], the TrØmso study[5], among others.[4,26–28]

We included 14 SNPs from the following genes: *CYP2R1* (rs10741657, rs2060793), *GC* (rs3755967, rs4588, rs7041, rs2282679), *DHCR7* (rs3794060, rs3829251, rs4944957,rs7944926,rs12800438),*LICN01768*(rs333966), and *CYP24A1* (rs6013897, rs17217119). Genotyping of rs4588, rs7041, rs2282679, rs2060793, rs333966, rs6013897, and rs17217119 were performed using qPCR with validated TaqMan® probes on a StepOnePlus™ Real-Time PCR system (Applied Biosystems, MA, USA). Approximately 10% of the samples were reanalyzed to confirm genotyping results. The remaining SNPs were genotyped using a Golden Gate® microarray (Illumina, San Diego, CA). The SNP information included in this study was based on the human genome assembly GRCh38/hg38 (*UCSC* Genome Browser).

Participants' genetic ancestry was determined from a previous study based on the genotyping of 96 ancestry-informative markers (unpublished data) and principal components were calculated using the EIGENSTRAT method [29].

Quality control: All samples and SNPs with more than 15% missing genotypes, SNPs with a minor allele frequency (MAF) < 5%, and those deviating from Hardy-Weinberg equilibrium (HWE, χ^2 test p = 0.004) were excluded from subsequent analyses.

Statistical analysis: Normality of the data was assessed using the Kolmogorov-Smirnov test. Data analyses exclusively regarding anthropometric, clinical, and biochemical variables were performed with IBM® SPSS Statistics v22.0 software (IBM Corp., Armonk, NY, USA). SNP data were analyzed with PLINK 1.9 (www.cog-genomics.org/plink/1.9/)[30] and data visualization were done with Jamovi (The jamovi project. J*amovi* v2.2. Sidney: 2023. (accessed October 17, 2023). Available from: https://www.jamovi.org). Odds ratios (OR), unstandardized regression coefficients (β), and 95% confidence intervals (CI) were calculated. *P*-values < 0.05 were considered statistically significant.

Logistic regression analyses using a backward elimination algorithm were performed with DM2 as the dependent variable and age, sex, plasma 25(OH)D levels, BMI, lipid profile, and AHT diagnosis as independent variables. A separate logistic regression analysis was conducted with glycemic status as the dependent variable, including the same set of predictors. One-way ANOVA was used to assess the probability that the model assigns a case based on participants' vitamin D status. HbA1c levels were not included as a predictor variable in these models, as they were used to define the categories of normoglycemic, prediabetic and diabetic individuals. Instead, the association between HbA1c and plasma 25(OH)D levels was evaluated using Pearson's correlation coefficient.

The association between genetic variants and DM2, as well as plasma 25(OH)D levels, was evaluated using logistic and linear regression models, respectively. Biochemical or clinical variables associated with plasma 25(OH)D levels and DM2 were included in the regression models. Multiple testing adjustments were made using the Bonferroni correction. Additionally, linkage disequilibrium and epistasis analyses were performed.

Results

Anthropometric, clinical, and biochemical characteristics of the study population: Characteristics of study subjects are presented in Table 1. In the non-DM2 group, 61% were overweight or obese, and 51% had a diagnosis for essential AHT. In the DM2 group, 89% of participants were overweight or obese, and 87% had AHT. Among study participants, 22.8% had sufficient vitamin D levels, 47.6% had insufficient levels and 29.6% were classified as deficient. The prevalence of sufficient vitamin D status was higher among individuals without DM2 (26.5%) compared to those with DM2 (19.5%). Conversely, vitamin D deficiency was more prevalent in participants with DM2 (36.4%) than among participants without DM2 (21.9%). Significant differences in vitamin D status were observed between the non-DM2 and DM2 groups (χ^2 = 14.36, df = 2, p = 0.0008).

Table 1. Anthropometric, biochemical, and clinical characteristics of participants with and without type 2 diabetes in the study

Variable	Non-DM2 (n= 262)	DM2 (n= 316)
Sex (*n*, %)		
Male	82 (31)	105 (33)
Female	180 (69)	211 (67)
Age (years)*	61.0 | 15.0	62.0 | 14.5
BMI**	26.9 ± 4.3	30.6 ± 5.6
Underweight (n, %)	3 (1)	0
Normal weight (n, %)	73 (28)	36 (11)
Overweight (n, %)	117 (45)	133 (42)
Obesity I (n, %)	41 (16)	85 (27)
Obesity II and III (n, %)	12 (5)	61 (19)
FPG (mg/dL)*	92.0 | 8.0	128.0 | 48.5
HbA1c (%)*	5.7 | 0.5	6.9 | 2.2
Normal glycemic status (n, %)	130 (50)	NA
Prediabetes (n, %)	132 (50)	NA
TC (mg/dL) *	203.0 | 51.0	191.0 | 55.0
TG (mg/dL) *	144.0 | 88.0	172.0 | 97.5
HDL (mg/dL) *	42.20 | 13.4	37.0 | 11.5
LDL (mg/dL) **	134.8 ± 36.7	115.6 ± 33.8
VLDL (mg/dL) *	29.2 | 17.4	34.4 | 19.9
Systolic BP (mmHg) *	125 | 24	135 | 26
Diastolic BP (mmHg) *	73 | 11	76 | 13
AHT (n, %)	133 (51)	275 (87)
25(OH)D (ng/mL)**	26.3 ± 7.4	23.4 ± 7.7

* Median | interquartile range; ** mean ± SD; NA: not applicable. DM2: type 2 diabetes; BMI= body mass index; FPG= fasting plasma glucose; HbA1c= hemoglobin A1C; TC= total cholesterol; TG= triglycerides; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein cholesterol; VLDL= very-low-density lipoprotein cholesterol; BP= blood pressure, AHT= arterial hypertension; 25(OH)D= 25-hydroxyvitamin D

Association of clinical, and biochemical variables with DM2: In our study, no significant association was observed between age or sex and DM2 (OR: 1.02, p = 0.198 and OR: 0.74, p = 0.229, respectively), likely reflecting the matching of cases and controls for these variables during recruitment. Table 2 shows clinical and biochemical variables associated with DM2. Plasma 25(OH)D levels, HDL, LDL, AHT, and BMI were significantly associated with DM2 (all-p values <0.05). Based on the observed ORs, the probability of being classified in the DM2 group was two times higher for hypertensive participants, 13% higher for each unit increase in BMI, and 3% lower for each unit (ng/mL) increase in plasma 25(OH)D levels. The mean predicted probability of being classified in the DM2 group, according to the model shown in Table 2, was 0.71 ± 0.21 for the vitamin D–deficient group, 0.57 ± 0.23 for participants with insufficient levels, and 0.47 ± 0.24 for those with sufficient vitamin D levels (p <0.001).

Table 2. Multivariate logistic regression analysis of significant clinical and biochemical variables associated with type 2 diabetes

Variable	OR (95% CI)	*p*
AHT	3.31 (2.04–5. 37)	<0.001
BMI	1.13 (1.07–1.18)	<0.001
25(OH)D	0.97 (0.94-0.99)	0.023
HDL	0.98 (0.96-0.99)	0.011
LDL	0.99 (0.98-0.99)	<0.001

The group of participants without type 2 diabetic was the reference category (n= 475). OR= odds ratio; CI= confidence interval; AHT= arterial hypertension; BMI= body mass index; 25(OH)D= 25-hydroxyvitamin D; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein cholesterol

Because some participants in the non-DM2 group exhibited abnormal HbA1c levels, the logistic regression model shown in Table 2 was applied separately for each glycemic status category. Table 3 shows a significant difference in the prevalence of ATH between normoglycemic and prediabetic subjects, with plasma 25(OH)D levels in the latter group approaching marginal statistical significance. Additionally, no differences were observed in BMI, HDL, or LDL between normoglycemic and prediabetic subjects (Table 3). In the comparison between normoglycemic and DM2 participants, all variables remained statistically significant (Table 3). Within the DM2 group, HbA1c levels was inversely correlated with plasma 25(OH)D concentrations (r = -0,144, p = 0.034).

Table 3. Multivariate logistic regression analysis with clinical and biochemical variables according to the participants´ glycemic status

Glycemic status	Variables	OR (95% CI)	*p*
Prediabetic	AHT	1.84 (1.02 – 3.34)	0.044
	BMI	1.04 (0.97 – 1.11)	0.300
	25(OH)D	0.96 (0.93 – 0.99)	0.050
	HDL	0.99 (0.97 – 1.02)	0.530
	LDL	1.01 (0.99 – 1.01)	0.170
DM2	AHT	4.59 (2.59 – 8.10)	<0.0001
	BMI	1.15 (1.08 – 1.23)	<0.0001
	25(OH)D	0.95 (0.91 – 0.98)	0.002
	HDL	0.97 (0.95 – 0.98)	0.012
	LDL	0.99 (0.98 – 0.99)	0.012

The reference category was normoglycemic status (n = 475). DM2: type 2 diabetic; OR= odds ratio; CI= confidence interval; AHT= arterial hypertension; BMI= body mass index; 25(OH)D= 25-hydroxyvitamin D; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein cholesterol.

Association between SNPs, plasma 25(OH)D levels, and DM2: After quality control, 12 SNPs met the established criteria, except for rs333966 and rs17217119, which were excluded from further analysis due to a genotyping rate below 85%. All SNPs tested in the *GC* gene were associated with plasma 25(OH)D levels (all *p* values <0.036, Table 4). Individuals homozygous for the minor alleles of statistically significant SNPs exhibited lower mean plasma 25(OH)D levels compared to those with other genotypes (Figure 1).

Table 4. Association between single nucleotide polymorphisms of genes involved in the vitamin D metabolism and plasma 25-hydroxyvitamin D levels of the participants

Gene	SNP	A1	A2	MAF	β	95% CI	*p*	adjusted *p* *
GC	rs4588	T	G	0.22	-2.88	-4.14 – -1.61	1.109e-05	0.0001
	rs3755967	A	G	0.20	-2.60	-3.86 – -1.35	5.938e-05	0.0008
	rs2282679	G	T	0.21	-2.65	-3.93 – -1.36	6.591e-05	0.0009
	rs7041	A	C	0.48	-1.63	-2.69 – -0.57	0.0028	0.0358
CYP2R1	rs2060793	A	G	0.30	1.42	0.20 – 2.64	0.0227	0.2972
	rs10741657	A	G	0.29	1.35	0.12 – 2.59	0.0324	0.4207
DHCR7	rs3829251	A	G	0.29	-1.12	-2.24 – 0.004	0.0516	0.6712
	rs3794060	T	C	0.48	0.91	-0.14 – 1.96	0.0886	1
	rs4944957	A	G	0.50	-0.90	-1.95 – 0.15	0.0919	1
	rs7944926	G	A	0.48	0.94	-0.10 – 1.98	0.0779	1
	rs12800438	A	G	0.50	0.87	-0.19 – 1.94	0.1095	1
CYP24A1	rs6013897	A	T	0.32	-0.66	-1.91 – 0.58	0.2969	1

Regression model adjusted by sex, age, BMI, genetic ancestry, and glycemic status. *Bonferroni correction. SNP= single nucleotide polymorphism; A1= minor allele; A2= alternative allele; MAF= minor allele frequency; β= unstandardized regression coefficient; CI= confidence interval

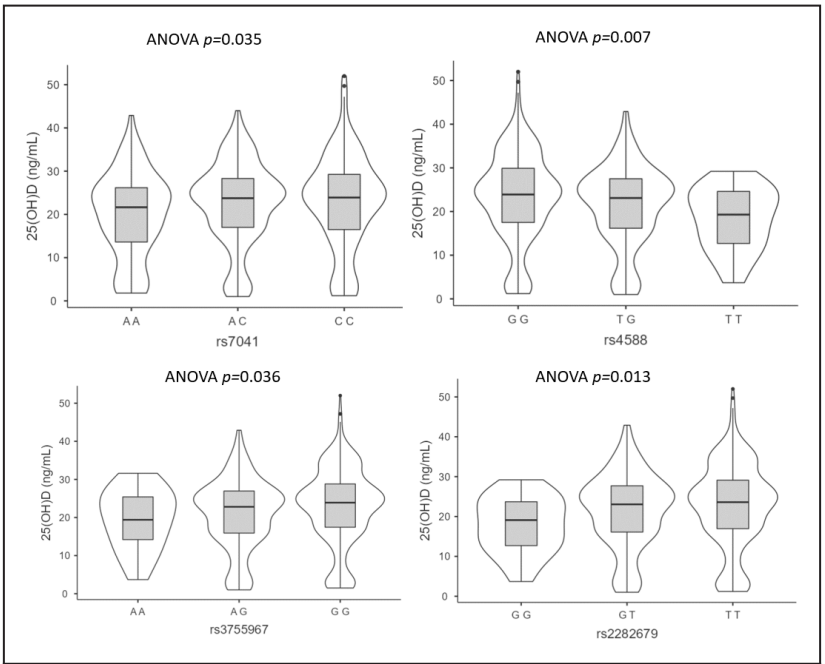

Figure 1. Mean plasma 25-hydroxyvitamin D levels according to genotypes of *GC* gene of single nucleotide polymorphisms associated with the plasma 25-hydroxivitamin D in participants with and without type 2 diabetes. The AA genotype of rs7041, TT of rs4588, GG of rs3755967, GG of rs2282679 showed less plasma 25-hydroxyvitamin D level than subjects with the other genotypes for this gene.

Following Bonferroni correction, none of the 12 SNPs demonstrated association with DM2 (all *p* values >0.05). Additionally, the epistasis analysis did not identify any significant interaction effects among the evaluated SNPs. Linkage disequilibrium was observed among rs4588, rs3755967, and rs2282679 (all R^2 >0.86).

Discussion

This is the first study to examine the association between genetic polymorphisms, plasma vitamin D levels, clinical variables, and DM2 in an urban sample of the Costa Rican population. The observed inverse association between 25(OH)D concentrations and DM2 risk in this population is consistent with findings from other cohorts, including NHANES-III study,[7] in which individuals of Latin American origin from the United States showed a similar inverse association.

In this sample, the prevalence of overweight/obesity and hypertension was high in both groups, and these two factors exhibited the strongest associations with the risk of DM2. In contrast, the effect of low plasma concentrations of 25(OH)D on DM2 risk was notably smaller than the impact of well-established risk factors such as hypertension, obesity, and dyslipidemia.[31,32] Using a logistic regression model, we estimated that a 3 ng/mL difference in plasma 25(OH)D levels—approximately the mean difference observed between the DM2 and the non-DM2 groups—was associated with an 8.4% increase in the risk of DM2. Although this effect size is modest, it remains epidemiologically relevant given that vitamin D status is a modifiable risk factor. Furthermore, the model demonstrated improved predictive performance when 25(OH)D concentrations were in the deficient range. These findings suggest that vitamin D deficiency may contribute to the overall risk profile for DM2 and that risk prediction models may be more accurate in populations with low vitamin D status.

Among participants with DM2, we observed a significant inverse correlation between plasma 25(OH) D levels and HbA1c, indicating that lower vitamin D status is associated with poorer glycemic control. Similarly, in a younger population from a university center in Costa Rica, a previous study reported that, despite a lower prevalence of vitamin D deficiency (25%) and reduced rates of obesity, lower 25(OH) D concentrations were correlated with markers of insulin resistance, such as HOMA-IR[33]. Together, these findings suggest a relationship between vitamin D status and markers of glucose metabolism across populations with varying metabolic risk profiles.

Our findings indicate that SNPs in the *GC* gene—rs4588, rs7041, rs3755967, and rs2282679—are associated with lower plasma 25(OH)D concentrations. These results are consistent with previous studies in Hispanic and Caucasian populations,[4–6] reinforcing the role of genetic variation in modulating vitamin D metabolism. Considering that approximately 0.01% of circulating 25(OH)D is present in its free form and that nearly all of it is bound to plasma proteins, primarily the GC,[34] SNPs that modulate *GC* gene expression or binding affinity likely influence total 25(OH)D levels and, consequently, vitamin D status. These genetic influences on vitamin D bioavailability may help explain interindividual variability in metabolic markers relevant to DM2, without implying a direct causal relationship between these polymorphisms and disease onset.

The most common isoforms of the *GC* gene (GC1f, GC1s, and GC2) are determined by the rs7041 and rs4588 polymorphisms. The A allele of rs7041 encodes Asp at position 416, which is present in both GC1f and GC2 isoforms, while the T allele of rs4588 encodes Lys at position 420 in the GC2 isoform. These amino acid substitutions modify the binding affinity of the GC protein for 25(OH)D,[35,36] thereby influencing its circulating levels. While rs3755967 and rs2282679 have also been associated with 25(OH)D concentrations, their functional role remains uncertain and may reflect linkage disequilibrium with rs4588. Notably, a study in Mexican postmenopausal women reported a similar association, as well as evidence of linkage disequilibrium between rs3755967 and rs2282679,[37] further supporting the contribution of *GC* gene variants to vitamin D status in different populations.

Although low plasma 25(OH)D levels were associated with DM2, none of the 12 SNPs analyzed showed a direct association with the disease. This observation is consistent with the multifactorial and progressive nature of DM2, in which the contribution of individual genetic variants to disease development is typically modest compared with that of established clinical and environmental risk factors. Nevertheless, low plasma 25(OH)D levels have been implicated in biological pathways involved in insulin resistance, polycystic ovary syndrome, and obesity,[38] all of which are recognized contributors to DM2 pathogenesis.

This study highlighted the potential role of 25(OH) D levels as a risk factor for DM2 in an understudied, admixed population, supporting previous findings in populations with different genetic backgrounds. However, our study presented limitations, particularly regarding the classification of glycemic status within the sample. In particular, the control group included individuals with HbA1c levels exceeding 5.7%, indicating

the inclusion of both normoglycemic and prediabetic subjects.[39] This distinction is clinically important, as glycemic categories are associated with varying risks for major cardiovascular events, such as myocardial infarction, stroke, and cardiovascular mortality.[40,41] To address this limitation, two complementary strategies were implemented: 1) reclassification of participants into normoglycemic, prediabetic, and diabetic groups; and 2) application of a logistic regression model incorporating these three categories. The model demonstrated slight differences between normoglycemic and prediabetic individuals, suggesting that, based on the variables included, these groups did not differ from each other.

In conclusion, this is the first study to examine the relationship between vitamin D status, genetic variants involved in vitamin D metabolism, and DM2 in an urban Costa Rican population. We observed an inverse association between plasma 25(OH)D levels and DM2 and identified *GC* gene variants associated with lower vitamin D concentrations. Although these variants were not directly linked to disease risk, they may contribute to interindividual variability in vitamin D metabolism. The inclusion of prediabetic participants in the non-DM2 group represents a limitation; however, complementary analyses using reclassified glycemic categories suggest that the main association remain consistent. Future studies should further explore the functional impact of these variants, consider longitudinal designs to clarify causal relationships, and investigate interactions with modifiable lifestyle factors in the development of DM2.

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The contribution of each author is as follows:

SMR: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. RVS: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Review & Editing. GGS: Conceptualization, Funding Acquisition, Supervision, Validation, Writing – Review & Editing.

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