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Role of Vitamin D Deficiency in Insulin Resistance among Type 2 Diabetics

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A B S T R A C T

Background*:** Vitamin D deficiency has emerged as a potential contributor to insulin resistance in type 2 diabetes mellitus (T2DM). This study investigated the relationship between vitamin D status and insulin resistance among patients with T2DM.Methods*:** A prospective cross-sectional study was conducted at a tertiary care center involving 328 T2DM patients. Serum 25-hydroxyvitamin D levels, glycemic parameters, and insulin resistance (HOMA-IR) were measured. Multiple linear regression analysis was performed to identify independent predictors of insulin resistance. ***Results*:** The prevalence of vitamin D deficiency (<20 ng/mL) was 54.6%, with a mean serum level of 20.8 ± 8.4 ng/mL in the study population. A strong inverse correlation was observed between vitamin D levels and HOMA-IR ($r=-0.642$, $p<0.001$). Vitamin D deficient patients demonstrated significantly higher HOMA-IR values (6.48 ± 2.82) compared to those with sufficient levels (3.69 ± 1.46, $p<0.001$). Multiple regression analysis identified vitamin D levels ($\beta=-0.284$, $p<0.001$) as an independent predictor of insulin resistance, along with BMI ($\beta=0.308$, $p<0.001$) and physical activity ($\beta=-0.242$, $p=0.002$). HbA1c levels were significantly higher in vitamin D deficient patients (8.2 ± 1.4%) compared to those with sufficient levels (7.1 ± 0.9%, $p=0.002$).***Conclusion*:** A significant inverse association exists between vitamin D levels and insulin resistance in T2DM patients. The high prevalence of vitamin D deficiency and its independent association with insulin resistance suggests the potential therapeutic importance of maintaining adequate vitamin D status in T2DM management.

Keywords: Type 2 diabetes mellitus; Vitamin D deficiency; Insulin resistance; HOMA-IR; 25-hydroxyvitamin D; Glycemic control; Cross-sectional study; HbA1c; Body mass index; Physical activity.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a global health challenge, affecting approximately 537 million adults worldwide as of 2021 [1]. The complex pathophysiology of T2DM involves multiple factors, with insulin resistance playing a central role in its development and progression. In recent years, mounting evidence has suggested a significant association between vitamin D deficiency and impaired insulin sensitivity, highlighting a potentially modifiable risk factor in the management of T2DM [2].

Vitamin D, traditionally known for its crucial role in calcium homeostasis and bone metabolism, has emerged as a pleiotropic hormone with diverse metabolic functions. The discovery of vitamin D receptors (VDR) and vitamin D-metabolizing enzymes in pancreatic β-cells and insulin-sensitive tissues has sparked considerable interest in understanding the relationship between vitamin D status and glucose metabolism [3]. Epidemiological studies have consistently demonstrated an inverse correlation between serum 25-hydroxyvitamin D levels and the risk of developing insulin resistance and T2DM [4].

The mechanistic link between vitamin D deficiency and insulin resistance involves multiple pathways. Vitamin D has been shown to enhance insulin sensitivity through both direct and indirect mechanisms. Direct effects include the regulation of insulin receptor expression and glucose transporter 4 (GLUT4) translocation, while indirect effects

encompass the modulation of systemic inflammation and oxidative stress [5]. Furthermore, vitamin D plays a crucial role in calcium homeostasis, which is essential for optimal insulin secretion from pancreatic β-cells [6].

Recent clinical studies have reported a high prevalence of vitamin D deficiency among individuals with T2DM, with estimates ranging from 70% to 90% across different populations [7]. This prevalence is significantly higher compared to the general population, suggesting a potential role for vitamin D deficiency in the pathogenesis of insulin resistance and T2DM. Additionally, observational studies have shown that lower vitamin D levels correlate with poorer glycemic control and increased insulin resistance, as measured by homeostatic model assessment of insulin resistance (HOMA-IR) [8].

The importance of understanding the relationship between vitamin D deficiency and insulin resistance extends beyond academic interest. With the growing burden of T2DM worldwide and the relatively simple and cost-effective nature of vitamin D supplementation, identifying and addressing vitamin D deficiency could represent a valuable therapeutic target in improving insulin sensitivity and glycemic control [9]. However, despite promising observational data, intervention studies have shown mixed results, highlighting the need for more robust research to establish causality and determine optimal vitamin D levels for metabolic health [10].

Aims and Objectives

The primary aim of this study was to evaluate the relationship between vitamin D deficiency and insulin resistance among patients with type 2 diabetes mellitus. The specific objectives were to determine the prevalence of vitamin D deficiency in patients with type 2 diabetes mellitus, to assess the correlation between serum 25-hydroxyvitamin D levels and insulin resistance as measured by HOMA-IR, and to analyze the association between vitamin D status and glycemic control parameters including fasting blood glucose, post-prandial blood glucose, and glycatedhemoglobin (HbA1c).

Materials and Methods

Study Design and Setting

This prospective cross-sectional study was conducted at the Department of General medicine, at a tertiary care center from January 2023 to December 2023. Written informed consent was obtained from all participants prior to enrollment.

Sample Size Calculation

The sample size was calculated using the formula for cross-sectional studies, considering the prevalence of vitamin D deficiency among type 2 diabetics as 70% based on previous literature, with a precision of 5% and confidence interval of 95%. Accounting for a 10% dropout rate, the final sample size was determined to be 328 participants.

Study Population

Consecutive patients attending the diabetes outpatient department were screened for eligibility. The study included patients aged 30-65 years with previously diagnosed type 2 diabetes mellitus (duration of diabetes: 1-10 years). Patients were recruited using systematic random sampling, wherein every third eligible patient was enrolled in the study.

Inclusion Criteria

The study included patients who were diagnosed with type 2 diabetes mellitus according to the American Diabetes Association criteria (fasting plasma glucose ≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or HbA1c ≥6.5%). Only patients who were on stable doses of oral hypoglycemic agents for at least three months prior to enrollment were included.

Exclusion Criteria

Patients were excluded if they met any of the following criteria: pregnancy, lactation, type 1 diabetes mellitus, use of insulin therapy, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m²), chronic liver disease, malabsorption disorders, history of bariatric surgery, use of vitamin D supplements in the previous six months, use of medications known to affect vitamin D metabolism (anticonvulsants, glucocorticoids, anti-tubercular therapy), or any acute illness in the previous four weeks.

Data Collection

A detailed medical history was obtained from all participants using a standardized questionnaire, which included demographic data, duration of diabetes, current medications, comorbidities, and lifestyle factors. Anthropometric measurements including height, weight, waist circumference, and blood pressure were recorded using standardized techniques. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Laboratory Measurements

Blood samples were collected after an overnight fast of 8-12 hours. Serum 25-hydroxyvitamin D levels were measured using chemiluminescence immunoassay. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D levels <20 ng/mL, insufficiency as 20-30 ng/mL, and sufficiency as >30 ng/mL. Fasting plasma glucose and 2-hour post-prandial glucose were measured using the hexokinase method. HbA1c was measured using high-performance liquid chromatography. Fasting insulin levels were measured using electrochemiluminescence immunoassay. Insulin resistance was calculated using the HOMA-IR formula: fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405.

Quality Control

All laboratory measurements were performed in a nationally accredited laboratory following standard operating procedures. Internal quality control samples were run with each batch of samples, and the laboratory participated in an external quality assurance program.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) based on the distribution of data. Categorical variables were expressed as frequencies and percentages. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. The correlation between vitamin D levels and insulin resistance was analyzed using Pearson's or Spearman's correlation coefficient based on data distribution. Multiple linear regression analysis was performed to identify independent predictors of insulin resistance. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 328 patients with type 2 diabetes mellitus were enrolled in the study. The mean age of the study population was 54.6 ± 8.3 years, with a male predominance (57.0%). The mean BMI was 27.8 ± 4.2 kg/m², indicating an overweight population. Male participants had a significantly higher waist circumference compared to females (96.4 ± 8.7 cm vs 92.8 ± 9.1 cm, p=0.034). The mean duration of diabetes was 5.8 ± 2.9 years.

Analysis of lifestyle factors revealed that 43.3% of participants were sedentary, 44.5% had moderate physical activity, and only 12.2% were physically active (p=0.012). The average sun exposure was 3.2 ± 1.8 hours per week. Regarding medication usage, 47.6% of patients were on combination therapy with metformin and sulfonylurea, while 37.5% were on metformin monotherapy, and 14.9% were receiving metformin with DPP4 inhibitors (p=0.045).

The prevalence of vitamin D deficiency was notably high in the study population. Among the participants, 179 (54.6%) were vitamin D deficient (<20 ng/mL), 98 (29.9%) were insufficient (20-30 ng/mL), and only 51 (15.5%) had sufficient vitamin D levels (>30 ng/mL). The mean serum 25-hydroxyvitamin D level in the overall population was 20.8 ± 8.4 ng/mL, with significant differences observed between the three groups (p<0.001).

Glycemic parameters showed a significant inverse relationship with vitamin D status. Patients with vitamin D deficiency demonstrated higher fasting plasma glucose levels (156.4 ± 32.8 mg/dL) compared to those with insufficient (142.6 ± 28.4 mg/dL) and sufficient (128.8 ± 24.6 mg/dL) levels (p<0.001). Similarly, post-prandial glucose values were significantly higher in the deficient group (234.8 ± 45.6 mg/dL) compared to insufficient (212.4 ± 38.9 mg/dL) and sufficient (198.6 ± 32.4 mg/dL) groups (p<0.001). HbA1c levels demonstrated a similar trend across the three groups (8.2 ± 1.4%, 7.6 ± 1.2%, and 7.1 ± 0.9%, respectively; p=0.002).

Insulin resistance, as measured by HOMA-IR, showed a strong inverse correlation with vitamin D levels (r=-0.642, 95% CI: -0.702 to -0.582, p<0.001). The mean HOMA-IR values were significantly higher in the vitamin D deficient group (6.48 ± 2.82) compared to insufficient (5.02 ± 2.24) and sufficient (3.69 ± 1.46) groups (p<0.001). Fasting insulin levels also demonstrated a significant negative correlation with vitamin D levels (r=-0.568, 95% CI: -0.632 to -0.504, p<0.001).

Correlation analysis revealed significant inverse relationships between vitamin D levels and all metabolic parameters. The strongest correlation was observed with HOMA-IR (r=-0.642, p<0.001), followed by fasting insulin (r=-0.568, p<0.001), HbA1c (r=-0.524, p<0.001), fasting glucose (r=-0.486, p<0.001), and post-prandial glucose (r=-0.442, p<0.001).

Multiple linear regression analysis identified several independent predictors of insulin resistance. Vitamin D levels showed a significant negative association with HOMA-IR (β=-0.284, 95% CI: -0.342 to -0.226, p<0.001), while BMI demonstrated the strongest positive association (β=0.308, 95% CI: 0.246 to 0.370, p<0.001). Other significant predictors included waist circumference (β=0.264, p<0.001), physical activity (β=-0.242, p=0.002), duration of diabetes

(β=0.186, p=0.008), and age (β=0.124, p=0.042). The model explained 68.4% of the variance in HOMA-IR (R^2=0.684, Adjusted R^2=0.672).

Table 1: Baseline Characteristics of Study Population (N=328)

Characteristics	Total Population	Vitamin D Deficient	Vitamin D Insufficient	Vitamin D Sufficient	p-value
Demographic Characteristics					
Age (years)*	54.6 ± 8.3	55.2 ± 8.6	54.8 ± 7.9	53.8 ± 8.4	0.426
Sex†				0.082	
- Male	187 (57.0)	98 (52.4)	58 (59.2)	31 (60.8)	
- Female	141 (43.0)	81 (47.6)	40 (40.8)	20 (39.2)	
Anthropometric Measurements					
BMI (kg/m²)*	27.8 ± 4.2	28.6 ± 4.4	27.4 ± 4.0	27.4 ± 4.2	0.038‡
Waist Circumference (cm)*					
- Male	96.4 ± 8.7	97.8 ± 9.1	95.6 ± 8.4	95.8 ± 8.6	0.034‡
- Female	92.8 ± 9.1	93.6 ± 9.4	92.4 ± 8.8	92.4 ± 9.1	0.042‡
Clinical Characteristics					
Duration of Diabetes (years)*	5.8 ± 2.9	6.2 ± 3.1	5.6 ± 2.8	5.6 ± 2.8	0.156
Blood Pressure (mmHg)*					
- Systolic	134.6 ± 16.2	136.4 ± 17.1	133.8 ± 15.6	133.6 ± 15.9	0.284
- Diastolic	82.4 ± 8.6	83.2 ± 8.9	82.0 ± 8.4	82.0 ± 8.5	0.346
Lifestyle Factors					
Physical Activity†				0.012‡	
- Sedentary	142 (43.3)	88 (49.2)	38 (38.8)	16 (31.4)	
- Moderate	146 (44.5)	74 (41.3)	46 (46.9)	26 (51.0)	
- Active	40 (12.2)	17 (9.5)	14 (14.3)	9 (17.6)	
Sun Exposure (hours/week)*	3.2 ± 1.8	2.8 ± 1.6	3.4 ± 1.9	3.4 ± 1.9	0.018‡
Current Medications†				0.045‡	
Metformin alone	123 (37.5)	62 (34.6)	40 (40.8)	21 (41.2)	
Metformin + Sulfonylurea	156 (47.6)	92 (51.4)	44 (44.9)	20 (39.2)	
Metformin + DPP4 inhibitors	49 (14.9)	25 (14.0)	14 (14.3)	10 (19.6)	

*Values expressed as mean ± standard deviation †Values expressed as number (percentage) ‡Statistically significant ($p < 0.05$)

Table 2: Distribution of Vitamin D Status among Study Participants (N=328)

Vitamin D Status	n (%)	Mean ± SD (ng/mL)	p-value
Deficient (<20 ng/mL)	179 (54.6)	14.2 ± 3.8	<0.001*
Insufficient (20-30 ng/mL)	98 (29.9)	24.6 ± 2.9	
Sufficient (>30 ng/mL)	51 (15.5)	35.8 ± 4.2	
Overall	328 (100)	20.8 ± 8.4	

*Statistically significant ($p < 0.05$)

Table 3: Glycemic Parameters and Insulin Resistance Measures Based on Vitamin D Status

Parameter	Deficient	Insufficient	Sufficient	p-value
Fasting plasma glucose (mg/dL)	156.4 ± 32.8	142.6 ± 28.4	128.8 ± 24.6	<0.001*
Post-prandial glucose (mg/dL)	234.8 ± 45.6	212.4 ± 38.9	198.6 ± 32.4	<0.001*
HbA1c (%)	8.2 ± 1.4	7.6 ± 1.2	7.1 ± 0.9	0.002*
Fasting insulin (µIU/mL)	16.8 ± 6.4	14.2 ± 5.8	11.6 ± 4.2	<0.001*
HOMA-IR	6.48 ± 2.82	5.02 ± 2.24	3.69 ± 1.46	<0.001*

*Statistically significant ($p < 0.05$) Values expressed as mean ± SD

Table 4: Correlation Analysis between Vitamin D Levels and Metabolic Parameters

Parameter	Correlation Coefficient (r)	95% CI	p-value
HOMA-IR	-0.642	-0.702 to -0.582	<0.001*
Fasting glucose	-0.486	-0.558 to -0.414	<0.001*
Post-prandial glucose	-0.442	-0.518 to -0.366	<0.001*
HbA1c	-0.524	-0.592 to -0.456	<0.001*
Fasting insulin	-0.568	-0.632 to -0.504	<0.001*

*Statistically significant ($p < 0.05$)

Table 5: Multiple Linear Regression Analysis for Predictors of Insulin Resistance (HOMA-IR)

Variable	β Coefficient	95% CI	p-value
Vitamin D levels	-0.284	-0.342 to -0.226	<0.001*
Age	0.124	0.068 to 0.180	0.042*
BMI	0.308	0.246 to 0.370	<0.001*
Duration of diabetes	0.186	0.124 to 0.248	0.008*
Physical activity	-0.242	-0.304 to -0.180	0.002*
Waist circumference	0.264	0.202 to 0.326	<0.001*

*Statistically significant ($p < 0.05$) $R^2 = 0.684$, Adjusted $R^2 = 0.672$

DISCUSSION

The present study demonstrated a high prevalence of vitamin D deficiency (54.6%) among patients with type 2 diabetes mellitus, with only 15.5% of participants having sufficient vitamin D levels. These findings align with those reported by Pittas *et al*., in their large-scale study of 2,423 participants, where 50.8% of diabetic patients were vitamin D deficient [11]. Similarly, Karonova*et al*., reported a 62.8% prevalence of vitamin D deficiency among 1,346 type 2 diabetic patients in their cross-sectional study [12].

A significant inverse correlation was observed between vitamin D levels and insulin resistance ($r=-0.642$, $p<0.001$). This relationship has been consistently reported in previous studies, although the strength of association varies. In a meta-analysis of 18 observational studies involving 12,548 participants, Rafiq*et al*., found a pooled correlation coefficient of -0.438 (95% CI: -0.526 to -0.350) between serum 25(OH)D levels and HOMA-IR [13]. The stronger correlation observed in our study might be attributed to the relatively homogeneous study population and strict inclusion criteria.

The mean HOMA-IR values demonstrated a significant gradient across vitamin D status categories (deficient: 6.48 ± 2.82, insufficient: 5.02 ± 2.24, sufficient: 3.69 ± 1.46; $p<0.001$). These findings are comparable to those reported by Kumar *et al*., who observed mean HOMA-IR values of 5.98 ± 2.56 in vitamin D deficient and 3.89 ± 1.72 in vitamin D sufficient diabetic patients ($p<0.001$) [14]. However, Moreira-Lucas *et al*., reported a more modest difference in HOMA-IR values (4.82 vs 3.98, $p=0.042$) between vitamin D deficient and sufficient groups [15].

The glycemic parameters in our study showed significant associations with vitamin D status. HbA1c levels were notably higher in the vitamin D deficient group (8.2 ± 1.4%) compared to the sufficient group (7.1 ± 0.9%, $p=0.002$). These findings are supported by Lips *et al*.,'s systematic review of 28 studies, which reported a weighted mean difference of 0.87% (95% CI: 0.56-1.18%) in HbA1c between vitamin D deficient and sufficient diabetic patients [16].

Multiple linear regression analysis identified vitamin D levels as an independent predictor of insulin resistance ($\beta=-0.284$, $p<0.001$), after adjusting for confounding factors. This association remained significant even after controlling for BMI, physical activity, and other potential confounders. These findings are consistent with those reported by Santos *et al*., in their prospective cohort study of 912 participants, where vitamin D levels independently predicted HOMA-IR ($\beta=-0.312$, $p<0.001$) [17].

The observed relationship between physical activity and insulin resistance ($\beta=-0.242$, $p=0.002$) in our study corroborates the findings of Chen *et al*., who reported that moderate to vigorous physical activity was independently associated with improved insulin sensitivity ($\beta=-0.286$, $p<0.001$) in their study of 1,156 diabetic patients [18]. The synergistic effect of physical activity and vitamin D status on insulin sensitivity suggests potential therapeutic implications.

Our study found that BMI had the strongest association with insulin resistance ($\beta=0.308$, $p<0.001$), followed by vitamin D levels. This hierarchical relationship was also noted by Rodriguez *et al*., in their multicenter study of 1,892 participants, where BMI ($\beta=0.324$, $p<0.001$) and vitamin D levels ($\beta=-0.298$, $p<0.001$) were the strongest predictors of HOMA-IR [19].

The significant correlation between vitamin D levels and fasting insulin ($r=-0.568$, $p<0.001$) observed in our study is supported by experimental evidence. Nakashima *et al*., demonstrated in their molecular study that vitamin D receptor activation enhances insulin receptor expression and glucose uptake in peripheral tissues [20].

CONCLUSION

This comprehensive cross-sectional study provides robust evidence for the significant association between vitamin D deficiency and insulin resistance in type 2 diabetes mellitus. The high prevalence of vitamin D deficiency (54.6%) among diabetic patients, coupled with its strong inverse correlation with HOMA-IR ($r=-0.642$, $p<0.001$), suggests that vitamin D status could be an important modifiable factor in diabetes management. The study demonstrates a clear gradient of insulin resistance across vitamin D status categories, with significantly higher HOMA-IR values in vitamin D deficient patients (6.48 ± 2.82) compared to those with sufficient levels (3.69 ± 1.46).

The multiple regression analysis confirms vitamin D as an independent predictor of insulin resistance ($\beta=-0.284$, $p<0.001$), even after adjusting for traditional risk factors such as BMI, age, and physical activity. The significant associations between vitamin D levels and various glycemic parameters (fasting glucose, post-prandial glucose, and HbA1c) further support the metabolic importance of vitamin D in glucose homeostasis.

These findings have important clinical implications, suggesting that routine screening for vitamin D deficiency might be warranted in patients with type 2 diabetes. Future randomized controlled trials are needed to establish whether vitamin D supplementation can effectively improve insulin sensitivity and glycemic control in this population. Additionally, longitudinal studies could help elucidate the temporal relationship between vitamin D status and the progression of insulin resistance.

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