Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/j4p5aq65

ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND GLYCEMIC CONTROL IN TYPE 2 DIABETES PATIENTS

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) remains a worldwide epidemic, with glycemic control serving as the cornerstone of care to prevent microvascular and macrovascular complications. This study aims to investigate the association between baseline vitamin D deficiency and changes in glycemic control parameters (particularly HbA1c and fasting blood glucose).

Methods: A prospective cohort study was conducted with 200 type 2 diabetes mellitus patients who visited Sarosh Hospital and Diagnostic Center, Muzaffarabad, Azad Jammu and Kashmir, Pakistan. Patients were divided into two groups at baseline based on their blood 25-hydroxyvitamin D (25(OH)D) levels: deficient (<20 ng/mL) and insufficient/sufficient (≥20 ng/mL). HbA1c and fasting plasma glucose (FPG) levels were measured at baseline, 3 monthsm and 6 months to assess glycemic management. Throughout the observation period, all patients maintained their usual anti-diabetic regimens without protocol-driven vitamin D administration to test the natural association. The statistical study used repeated measures ANOVA and multivariate regression to control for confounding variables like age, body mass index (BMI), and baseline HbA1c.

Results: Among the 200 patients (mean age 54.7 ± 9.2 years; 52% male), 112 (56%) were vitamin D deficient at baseline. The deficient group had significantly higher mean HbA1c levels at baseline (8.4% ± 1.1%) than the non-deficient group (7.6% ± 0.9%) ($p < 0.001$). During the 6-month follow-up, the deficient group observed poor glycemic control, with HbA1c increasing to 8.7% ± 1.2%, whereas the non-deficient group remained stable (7.7% ± 1.0%). There was a strong negative association with HbA1c change at 6 months ($r= -0.42$, $p <0.001$). After controlling for age, gender, BMI, and baseline anti-diabetic medication use, multivariate regression analysis revealed that baseline vitamin D deficiency was an independent predictor of impaired glycemic progression ($\beta = 0.35$, $p= 0.002$).

Conclusion: Vitamin D deficiency is common among type 2 diabetes mellitus patients and is independently associated with poorer glycemic control and a progressive worsening of HbA1c over 6 months. These findings show that screening for and treating vitamin D deficiency could be an important adjuvant technique in diabetes care.

Keywords: Type 2 Diabetes; Vitamin D Deficiency; Glycemic Control; Glycated Hemoglobin; Blood Glucose

Introduction

Ineffective pancreatic β-cell response, insulin insensitivity, and chronically high blood glucose are usually associated with type 2 diabetes mellitus (T2DM), a global health issue. Over 537 million adults globally are affected, and numbers are anticipated to rise in the next decade [1].

Diabetes management requires glycemic control to reduce macrovascular and microvascular effects. Still, many patients are poorly controlled despite therapy advancements [2]. Vitamin D, a fat-soluble secosteroid, is well recognized for bone health but is also important in glucose metabolism and insulin signaling [3].

Metabolite 25 (OH)D stimulates vitamin D receptors in pancreatic β-cells and peripheral tissues, impacting insulin production, secretion, and sensitivity [4]. Its immunomodulatory and anti-inflammatory activities relate to T2DM aetiology [5].Low serum 25(OH)D are linked to high Hb1Ac, glucose intolerance, and insulin resistance. Patients with diabetes often have hypovitaminosis D, which may be associated to poor glycemic management [6]. Interventional study outcomes are inconclusive due to baseline vitamin D status, intervention dose, and follow-up duration heterogeneity [7].Many previous studies ignore confounding variables like body mass index, disease duration, and insulin use. Because vitamin D can be modified to improve diabetic management, this association must be clarified [8].Cross-sectional study designs cannot determine temporality, and short-term interventional studies may not reflect the natural trend in glycemic control associated with vit. D levels over the course of time. The variability of study populations, definitions of deficiency, and supplementing techniques makes it difficult to determine if vitamin D deficiency is a sign of poor health or a direct predictor of glycemic results. Clinical practice requires understanding how baseline vitamin D status affects short-t-medium-term glycemic stability since type 2 diabetes mellitus is chronic.Thus, this prospective cohort study examined the association between baseline vitamin D deficiency and 6-month glycemic control changes in 200 type 2 diabetes mellitus patients. Independent of other variables, we expected that vitamin D deficiency at baseline would result in worse glycemic control and worsening HbA1c over the 6-month follow-up period.

Material and Methods

This 6-month prospective, observational cohort study was conducted at the Department of Endocrinology at Sarosh Hospital and Diagnostic Center, Muzaffarabad, AJK, Pakistan, from January 2025 to June 2025. The institutional review board authorized the study protocol, and all subjects gave written informed consent before enrollment. The study followed Helsinki Declaration guidelines.

An outpatient endocrinology clinic enrolled 200 patients [9] with a verified diagnosis of type diabetes mellitus (HbA1c ≥ 125 mg/dL) according to American Diabetes Association guidelines. Adults 30-75 years old with T2DM for at least one year and stable anti-diabetic therapy (no changes in oral hypoglycemic agents or insulin class or dosage) for at least three months before inclusion. Type 1 diabetes, pregnancy, lactation, chronic kidney disease, malabsorption syndromes, vitamin D supplement use within 3 months, medications affecting vitamin D metabolism, or active malignancy. At the outset, demographic information such as age and gender, anthropometric measurements (height, weight and BMI_ amd lifestyle factors like sun exposure and physical activity were collected. The medical history, including the duration of diabetes and current medications, was collected from the patient's record.Fasting blood samples were obtained after an overnight fast (8-10 hours) at baseline, 3 months and 6 months. Serum 25(OH)D levels were measured to determine baseline vitamin D status, with deficiency defined as <20 ng/mL. Study participants were then divided into groups. Glycemic control was assessed by HbA1c and fasting plasma glucose (FPG). Further baseline tests, such as serum creatinine, calcium, albumin, and parathyroid hormone (PTH), were used to evaluate renal function and metabolic status.Patients received standard clinical care and anti-diabetic drugs during the six-month research. No vitamin D supplementation was given in the trial to observe the natural association between endogenous vitamin D status and glycemic progression. The primary outcome was the difference in baseline to six-month HbA1c between deficient and non-deficient groups. Secondary outcomes included fasting plasma glucose changes and the percentage of patients in each group with a clinically meaningful glycemic control worsening (defined as ≥ 0.5% HbA1c

increase from baseline).Data were analysed using IBM SPSS version 27.0. Continuous variables were analysed for normality using the Shapiro-Wilk test and reported as mean ± SD or median with IQR. Frequencies and percentages represented categorical variables. We compared baseline characteristics of the deficient and non-deficient groups using an independent t-test for continuous variables and chi-square tests for categorical variables. The longitudinal changes in HbA1c and FPG across groups were examined using repeated measures analysis of variance (ANOVA), with time as the within-subject factor and vitamin D status as the between-subject factor. Multivariate linear regression was used to determine the independent association between baseline vitamin D level and 8-month glycemic control. The dependent variable was the change in HbA1c from baseline to 6 months. Deficient or non-deficient baseline vitamin D status, age, sex, BMI, diabetes duration, baseline HBA1c, and number of anti-diabetic drugs were independent variables. Statistical significance was defined as p-value <0.05.

Results

Table 1 shows baseline characteristics. Out of 200 patients, 56% had vitamin D deficiency (<20 ng mL) and had a longer duration of diabetes (8.5 ± 3.2 years versus 6.9 ± 2.8 years; p=0.01). Baseline characteristics, including age (54.7 ± 9.2 years) and gender (52% were male). Patients with vitamin D deficiency had a significantly longer mean duration of diabetes (8.5 ± 3.2 years versus 6.9 ± years) and a higher mean body mass index (30.1 ± 4.5 kg.m^2 versus 28.3 ± 3.9 kg/m^2 with a p-value of 0.003 than the deficient group. The deficient group had significantly worse Vaseline glycemic indices, including higher mean HbA1c (8.4± 1.1versus 7.6 ± 0.9 with a p-value of 0.001) and fasting plasma glucose (162 ± 28 mg/dL versus 145 ± 22 mg/dL with a p-value of 0.001).

Table 1: Baseline Characteristics of Patients

Parameter	**Vitamin D Deficient (<20 ng/mL) (n=112)**	**Non-Deficient (≥20 ng/mL) (n=88)**	**p-value**
Age (years)	55.1 ± 9.5	54.2 ± 8.9	0.48
Male Sex (%)	58 (51.8%)	46 (52.3%)	0.94
BMI (kg/m²)	30.1 ± 4.5	28.3 ± 3.9	0.003
Diabetes Duration (years)	8.5 ± 3.2	6.9 ± 2.8	0.01
Baseline HbA1c (%)	8.4 ± 1.1	7.6 ± 0.9	<0.001
Baseline FPG (mg/dL)	162 ± 28	145 ± 22	<0.001
25(OH)D (ng/mL)	14.2 ± 3.1	26.8 ± 5.4	<0.001
Number of OHA/Insulin	2.1 ± 0.8	1.9 ± 0.7	

Patients with vitamin D deficiency showed a decline in glycemic control over 6 months, with mean HbA1c rising from 8.4 ± 1.1% at baseline to 8.7 ± 1.2% at 6 months (p-value=0.03). In comparison, the non-deficient group had stable HbA1c values *7.6 ± 0.9% to 7.7 ± 1.0% with a p-value of 0.41). A significant group-by-time interaction (F=5.82, p=0.004) showed vitamin D status affected HbA1C trends. Similarly, fasting plasma glucose increased considerably in the deficient group (162 ± 28 to 171 ± 30 mg/dL with a p-value of 0.002) while maintaining stable in the non-deficient group (145 ± 22 to 148 ± 24 mg/dL with a p-value of 0.29. These findings suggest that vitamin D deficiency worsens glycemic outcomes over time.

Table: Longitudinal Changes in Glycemic Parameters by Vitamin D Status

Parameter	Time Point	Vitamin D Deficient Group	Non-Deficient Group	p-value (Trend)
HbA1c (%)	Baseline	8.4 ± 1.1	7.6 ± 0.9	
	3 Months	8.6 ± 1.2	7.6 ± 1.0	
	6 Months	8.7 ± 1.2	7.7 ± 1.0	
	Within-group trend	p = 0.03	p = 0.41	
Fasting Plasma Glucose (mg/dL)	Baseline	162 ± 28	145 ± 22	
	6 Months	171 ± 30	148 ± 24	
	Within-group trend	p = 0.02	p = 0.29	
Between-group Comparison	HbA1c (Group × Time Interaction)			F = 5.82, p = 0.004

Figure 1 shows the clinically significant deterioration in glycemic control, as measured by a ≥0.5% increase in HbA1c from start to 6 months. Specifically, 38.4% deficient individuals met the criterion, while only 20.5% non-deficient patients did ($X^2 = 7.48$ with a p-value of 0.006).

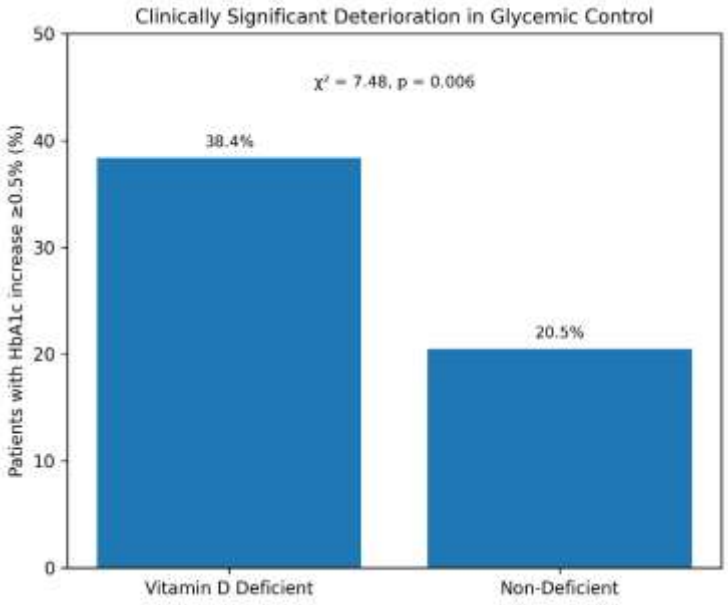

Figure 1: Clinically Significant Deterioration in Glycemic Control

Table 3 shows multiple regression analysis for ΔHbA1c (6 months). A regression model indicates that vitamin D insufficiency leads to a significant increase in HbA1c over 6 months (β= 0.35, p=0.002), indicating poorer glycemic control. BMI (p=0.03) and diabetes duration (p=0.01) also predict HbA1c rise. Age, gender, baseline HbA1c, and medication number were not significant (p>0.05). The regression model accounts for 28% of HbA1c change variability ($R^2 = 0.28$), indicating moderate explanatory power.

Table 3: Multiple Linear Regression Analysis for ΔHbA1c (6 Months)

Variable	**β Coefficient**	**95% Confidence Interval**	**p-value**

Vitamin D Deficiency (vs. Non-deficient)	0.35	0.13 – 0.57	0.002
Age (years)	-0.08	-0.21 – 0.05	0.24
Male Sex	0.05	-0.12 – 0.22	0.55
BMI (kg/m²)	0.19	0.02 – 0.36	0.03
Diabetes Duration (years)	0.22	0.05 – 0.39	0.01
Baseline HbA1c (%)	0.11	-0.07 – 0.29	0.22
Number of Anti-diabetic Meds	0.09	-0.10 – 0.28	0.35

Discussion

This prospective cohort study involving 200 patients with T2DM demonstrates that vitamin D deficiency is not just a comorbid disease but is independently associated with inferior glycemic control and a progressive deterioration of HbA1c over a 6-month duration. This study indicated that over half (56%) of the T2DM population in this study exhibited vitamin D deficiency, aligning with the elevated prevalence rates documented in other studies, which range from 40-80% based on geographic region and ethnicity [10,11]. The longitudinal glycemic control difference between deficient and non-deficient patients is the most considerable conclusion of this study. For 6 months, the deficient group had rising HbA1c levels, but the non-deficient group did not. This is critically relevant since vitamin D deficiency may be a risk factor for hyperglycemia development even in stable anti-diabetic individuals. The significant difference in clinical outcomes (≥0.5% increase in HbA1c level) between 38.4% of deficient individuals and 20.5% of non-deficient individuals highlights the potential impact of this phenomenon. Large-scale trials like the UKPDS have associated a 0.5% increase in HbA1c with a considerable increase in microvascular problems [12]. The association is biologically probable. The pancreatic β-cell converts 25 (OH)D to its active form, 1,25-dihydroxyvitamin D (calcitriol), by expressing the vitamin D receptor (VDR) and 1-hydroxylase enzyme. Calcitriol regulates calcium influx and insulin-related gene expression to regulate insulin production [13-15]. In deficiency, this pathway may be disrupted, resulting in improper insulin response to glucose stimuli [16]. Vitamin D deficiency also causes chronic low-grade inflammation and elevated parathyroid hormone (PTH_ levels, which increase peripheral tissue insulin resistance [17-19]. Vitamin D increases insulin sensitivity in skeletal muscle by upregulating the insulin receptor and promoting glucose transport, according to mechanistic studies [20]. In this study, it was found that vitamin D deficiency worsens glycemic control independently of BMI and diabetes duration in this multivariate regression analysis. Due to vitamin D accumulation in adipose tissue, obesity is a risk factor for both vitamin D deficiency and poor glycemic control. This study revealed that vitamin D's effect on hyperglycemia progression is not only due to obesity, but also by controlling for body mass index. This study supports an observational study associating low vitamin D with worse glycemic outcomes [21,22]. However, this prospective study, which includes repeated HbA1c measurements over 6 months, increases the evidence for temporality. Krul-Poel et al. found heterogeneity in interventional research, with some randomized controlled trials indicating a benefit of vitamin D supplementation on insulin resistance and others not [23]. These study findings indicate that the inability to show an effect in some trials may be related to short follow-up periods, low dose, or the inclusion of patients with only minor deficiency. The 6-month timeframe of this study provided ample time for divergence to emerge. This study has several strengths. First, the prospective design with a 6-month follow-up develops temporality, an enhancement over a cross-sectional study. Second, 200 samples had enough power to identify clinically significant changes. Third, by removing baseline vitamin D supplement users and not supplying them during the study, we were able to examine glycemic control during vitamin D status changes without intervention bias. Limitations must be

considered when interpreting the outcomes. This single-center study may not apply to people with varying genetics, diets, and sun exposure [24].

Conclusion

In this prospective cohort study of 200 patients with type 2 diabetes, vitamin D deficiency was common and independently associated with a significant gradual deterioration in glycemic control. Patients with vitamin D deficiency had a higher HbA1c level and were more likely to have a clinically significant worsening of their diabetes treatment than those with adequate levels. These findings indicate the potential usefulness of monitoring and managing vitamin D status as part of comprehensive diabetes management. Future large-scale, long-term randomized controlled trials are needed to observe if vitamin D treatment can successfully capture or reverse the deterioration in glycemic control and lower the burden of diabetes-related comorbidities.

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