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The Association Between Serum 25-hydroxyvitamin D and Glycemic Control in Patients With Diabetes Mellitus: A Single-Center Retrospective Study*

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Abstract

Objective. To determine the association between serum 25-hydroxyvitamin D (25(OH)D) and measures of glycemic control, hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG), in adult patients with diabetes mellitus.

Methodology. This is an analytical cross-sectional study of 270 patients with diabetes admitted to a tertiary hospital. Serum 25(OH)D levels were categorized as follows: sufficient (>30 ng/mL), insufficient (20 to 30 ng/mL), and deficient (<20 ng/mL). The correlation of HbA1c and FPG with serum 25(OH)D and other variables was determined using Spearman's rho (ρ) coefficient. The risk factors associated with HbA1c ≥7% and FPG ≥126 mg/dL were determined using logistic regression analysis to generate crude and adjusted odds ratios. The null hypothesis was rejected at 0.05 α-level of significance.

Results. The median serum 25(OH)D was 18.92 (range 3.56–56.3) ng/mL. Ninety percent (245 patients) had vitamin D levels below 30 ng/mL. This study showed that vitamin D level is significantly but weakly correlated with patient's age (ρ=0.339) and duration of diabetes (ρ=0.147), whereas it had inverse correlations with BMI (ρ=-0.134), HbA1c (ρ=-0.261), and FPG (ρ=-0.198).

Conclusion. In this study, we found a possible association between vitamin D levels and measures of glycemic control among this group of adult Filipino patients with diabetes mellitus, but further investigations in other cohorts of individuals with diabetes are needed.

Key words: Vitamin D, serum 25(OH)D, diabetes mellitus, glycemic control

INTRODUCTION

Diabetes mellitus is a complex and progressive metabolic disease. Its classification includes type 1 diabetes which involves immune-mediated destruction of the pancreatic β-cell, and type 2 diabetes characterized by relative insulin deficiency, pancreatic β-cell dysfunction, and peripheral resistance.[1] Diabetes mellitus has been a global health concern affecting millions of individuals, requiring continuous medical care with risk-reduction strategies beyond glycemic control.

Numerous data suggests that vitamin D has a pivotal role in regulating insulin secretion, insulin signaling, and improvement of insulin resistance by mediating the regulation of intracellular calcium levels.[2-4] Various cellular mechanisms in diabetes mellitus influence the metabolic signaling cascades, creating a causal link between metabolic stress and systemic inflammation.[5] Vitamin D indirectly serves an anti-inflammatory role by its effects on the cells of the immune system that secrete the pro-inflammatory cytokines which contribute to insulin resistance and autoimmune-mediated destruction of the β-cells.[4,6]

The status of vitamin D is determined by measuring serum 25(OH)D.[4,7] Studies suggest that an inverse relationship exists between vitamin D levels and measures of glycemic control, such as HbA1c and FPG.[2] In addition, a low level of vitamin D is associated with increased incidences of abdominal obesity, cerebrovascular diseases, myocardial infarction, and metabolic syndrome.[3,4]

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Vitamin D deficiency seems prevalent in Asia, with more than 50% of the population having vitamin D deficiency, while approximately 75% have insufficiency.[3] In a study of South Asian women, patients with insulin resistance and vitamin D deficiency were treated with vitamin D, 4000 IU/day. In this study, participants who achieved serum 25(OH)D above 32 ng/mL showed significant improvement in insulin sensitivity, thereby improving glycemic control.[3]

The 8th National Nutrition Survey (NNS) in 2013 showed that Filipino adults had a high prevalence of low vitamin D levels; vitamin D deficiency and insufficiency had a combined prevalence of 48.7% and were predominant in the National Capital Region (NCR).[8] This implies that Filipinos are at risk for hypovitaminosis D. Sufficient serum 25(OH)D level has been associated with optimal bone mineral density, muscle strength, and prevention of fractures.[9-11] Screening for vitamin D status is important to public health.

Due to the link between vitamin D levels and glucose homeostasis, screening for vitamin D deficiency and insufficiency in individuals with elevated HbA1c should be considered.[2,4,7] Moreover, supplementing low vitamin D levels may be an adjunctive treatment in managing diabetes, but further studies are still needed.[12] This study aims to determine the association between serum 25-hydroxyvitamin D [25(OH)D] and measures of glycemic control (HbA1c and FPG) in adult patients with diabetes mellitus.

METHODOLOGY

This study was approved by the Institutional Review Board (IRB) of the Makati Medical Center. The authors adhered to the ethical considerations set out in relevant guidelines, including the Declaration of Helsinki and the National Ethics Guidelines for Health Research and Data Privacy Act of 2012. The investigators completed the Good Clinical Practice (GCP) training on the responsible conduct of research with human data.

This cross-sectional analytical study was conducted in a private tertiary hospital in Metro Manila, Philippines. A retrospective review of the medical records of the study population from January 1, 2017 to June 30, 2021 was conducted. Convenience sampling was used for data collection.

In this study, patients were included if they had the following: (1) Serum 25(OH)D assay, HbA1c, and FPG done during admission at the study institution; (2) Normal serum total calcium or ionized calcium levels.

Patients were classified as having diabetes mellitus if they had at least one of the following criteria: (1) Diagnosed with diabetes mellitus type 1 or 2 based on medical records; (2) Use of oral and/or injectable anti-diabetic medications; (3) Previous laboratory results which included at least one of the following criteria: FPG ≥126 mg/dL; random plasma glucose ≥200 mg/dL with signs of polyuria, polydipsia or weight loss; 2-hour oral glucose tolerance test (OGTT) ≥200 mg/dL or HbA1c ≥6.5% [American Diabetes Association (ADA)].[13]

Since this is a retrospective review, the exposure to sunlight, physical activity, and dietary habits of the patients were not investigated.

The exclusion criteria were as follows: (1) Age less than 18 years old; (2) Patients with no available serum 25(OH) D assay and no serum total calcium or ionized calcium levels; (3) Pregnant or breastfeeding patients; (4) Patients with any acute or chronic blood loss, hemolytic anemia and known hemoglobin variants; (5) Patients with chronic liver disorder, chronic kidney disease or end-stage renal disease; (6) Patients with bone-mineral disorders such as but not limited to hypercalcemia, secondary osteoporosis, and hyperparathyroidism; (7) Patients taking calcium and vitamin D supplements before admission; (8) Intake of any other medications that may interfere with vitamin D metabolism such as glucocorticoids, antiestrogen, antiresorptive medications, and bisphosphonates; (9) Patients who underwent removal of any of the parathyroid glands.

Sample size

The sample size was computed using an online calculator from the University of California San Francisco, Clinical and Translational Science Institute (http://www.sample-size.net/correlation-sample-size/). Based on the study of Alkhatatbeh et al., the correlation of 25(OH)D levels with HbA1c and FPG levels was -0.23 and -0.17, respectively.[1] Assuming that the same results were obtained and using the power of 80% at 95% confidence level and accounting for 10% attrition rate, results showed that the sample size required for determining the correlation of serum 25(OH) D levels with HbA1c and FPG levels were 146 and 269, respectively. The final sample size was 299. A total of 1349 records were reviewed in this study. A total of 270 participants were included and analyzed (Figure 1).

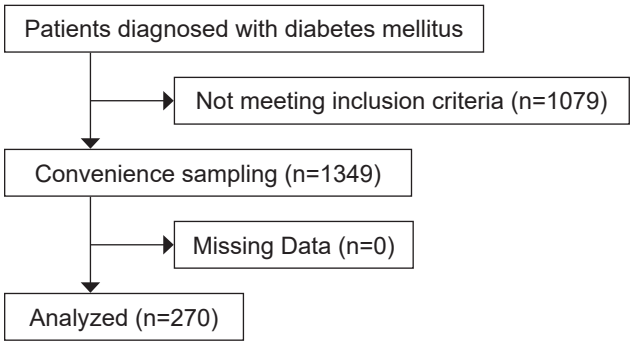

Figure 1. Flow diagram of patients included in the study.

Evaluation of vitamin D levels and glycemic control

In this study, the vitamin D status was determined by measuring the serum 25(OH)D levels. The classification of vitamin D levels was categorized as follows: sufficient (>30 ng/mL), insufficient (20 to 30 ng/mL), and deficient (less than 20 ng/mL).[4,7]

HbA1c is a glycemic target that needs to be individualized based on several factors: age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia, and adherence to therapy. According to the 2021 ADA guidelines, the achievement of HbA1c levels less than the goal of 7% may be acceptable and even beneficial if it can be safely achieved without significant hypoglycemia or other treatment adverse effects.[13] However, HbA1c goals of less than 8% may be appropriate for selected patients with limited life expectancy, or when the harms of treatment outweigh the benefits.[12,13] HbA1c is an integrated measurement of fasting and post-meal blood glucose levels during the preceding 6 to 8-week period.[12] The therapeutic plan depends on the physician's judgment and the patient's preference.

The FPG correlates with mean daily plasma glucose but may not be representative of long-term glycemic control compared to HbA1c. Diabetes mellitus is diagnosed at FBS ≥126 mg/dL on two separate samples.[13] However, acute stress, illness, and infection can increase glucose production and impair its utilization, thereby increasing fasting glucose.[14]

Statistical analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Shapiro-Wilk and Levene's tests were used to determine the normal distribution and homogeneity of variance of continuous variables, respectively. Continuous data which follow the normal distribution were summarized using mean and standard deviation, while non-Gaussian variables were reported as median and range. Categorical variables were reported as frequency and proportion.

Continuous variables that satisfied the dual assumptions of normal distribution and variance homogeneity were compared using an independent t-test. If both assumptions were violated, the non-parametric Kruskal-Wallis H test was used for comparison. The Chi-square test was used to compare categorical variables. If the expected percentages in the cells are less than 5%, Fisher's Exact Test was used instead.

Spearman's rho (ϱ) coefficient was used in determining the correlation of HbA1c and FPG with variables such as age, BMI, duration of diabetes, and vitamin D. According to Evans, less than 0.20 is very weak, 0.20 to 0.39 is weak, 0.40 to 0.59 is moderate, 0.60 to 0.79 is strong, and 0.80 or greater is a very strong correlation.[15] The variables associated with HbA1c ≥7% and FPG ≥126 mg/dL were determined using logistic regression analysis. The crude odds ratios (OR) and their corresponding 95% confidence intervals were estimated. Potential confounders (age, sex, BMI, hypertension, smoking history, alcohol drinking, and serum total cholesterol) were included in the multivariable model. Adjusted odds ratios and their 95% confidence intervals were reported. The null hypothesis was rejected at 0.05 α-level of significance. STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

The study included 270 adult patients with diabetes. The mean age was 57 ± 16 years with a slight female preponderance (56%) (Table 1). The median BMI was 26.7 kg/m^2, and more than a third were obese (38.5%). A majority had a diabetes duration of 1 to 10 years (60%), without a history of smoking (68%) or alcohol drinking (65%). Hypertension (66%) was the most common comorbidity, followed by dyslipidemia (35%).

The median serum 25(OH)D was 18.92 (range 3.56–56.3) ng/mL. 57% (n=155) were vitamin D deficient, 33% (n=90) were insufficient, while 10% (n=26) had sufficient vitamin D levels. Age was shown to be progressively lower with more deficient levels of vitamin D. Patients below 60 years comprised significantly more of the vitamin D deficient (66%) than insufficient (51%) patients, and more of the insufficient than sufficient (23%) patients. BMI was likewise seen to decrease with more sufficient levels of vitamin D. The median values of BMI in kg/m^2 were 27.55, 26.71, and 24.58 in the vitamin D deficient, insufficient, and sufficient groups, respectively. There were more patients with hypertension (88% vs. 60%) among the vitamin D sufficient versus deficient patients.

The median levels of HbA1c, FPG, and LDL-C among patients were elevated, whereas those for total cholesterol, triglyceride, and HDL-C were within normal ranges (Table 2). HbA1c was shown to be progressively lower with more sufficient levels of vitamin D. The median HbA1c levels were 9.76%, 7.7%, and 6.88% in the deficient, insufficient, and sufficient vitamin D groups, respectively. The median FPG was significantly higher among vitamin D deficient (173.71 mg/dL) than among insufficient (141.46 mg/dL) patients.

The vitamin D level was significantly but weakly correlated with the patient's age (ϱ=0.339) and duration of diabetes (ϱ=0.147), whereas it had inverse correlations with BMI (ϱ= -0.134), HbA1c (ϱ=-0.261), and FPG (ϱ =-0.198) (Table 3).

Age, smoking, and total cholesterol were found to be associated with elevated HbA1c, even after adjusting for covariates (Table 4). Vitamin D was crudely associated with elevated HbA1c; specifically, patients who had vitamin D deficiency were 4.484 times (95% CI 1.89 to 10.64) as likely

Table 1. Clinical and demographic profile of patients with diabetes mellitus

	All (n=270)	HbA1c <7% (n=79)	HbA1c ≥7% (n=191)	*p*
	Mean ± SD; Frequency (%); Median (Range)			
Age, years	56.19 ± 16.05	64.44 ± 15.94	52.77 ± 14.84	<0.001*
<60	154 (57.04)	29 (36.71)	125 (65.45)	
>60	116 (42.96)	50 (63.29)	66 (34.55)	
Sex				0.268†
Male	120 (44.44)	31 (39.24)	89 (46.6)	
Female	150 (55.56)	48 (60.76)	102 (53.4)	
Weight, kg [n=267]	70 (39–163)	69 (39–120)	71.5 (40–163)	0.326‡
Height, cm [n=267]	161 (120–180)	160 (143.5–179)	161.77 (120–180)	0.618‡
BMI, kg/m^2 [n=267]	26.71 (16.23–80.71)	25.74 (16.23–80.71)	27.08 (16.79–63.89)	0.928‡
Underweight	7 (2.62)	2 (2.53)	5 (2.66)	
Normal	75 (28.09)	21 (26.58)	54 (28.72)	
Overweight	81 (30.34)	24 (30.38)	57 (30.32)	
Obese I	51 (19.1)	16 (20.25)	35 (18.62)	
Obese II	19 (7.12)	4 (5.06)	15 (7.98)	
Obese III	34 (12.73)	12 (15.19)	22 (11.7)	
Blood pressure, mmHg				
Systolic	130 (79–214)	130 (90–190)	130 (79–214)	0.656‡
Diastolic	80 (50–134)	80 (60–100)	80 (50–134)	0.161‡
Smoking history				0.600†
No	183 (67.78)	55 (69.62)	128 (67.02)	
Current	33 (12.22)	11 (13.92)	22 (11.52)	
Former	54 (20)	13 (16.46)	41 (21.47)	
Alcohol drinker				0.825§
No	175 (64.81)	51 (64.56)	124 (64.92)	
Current	81 (30)	23 (29.11)	58 (30.37)	
Previous	14 (5.19)	5 (6.33)	9 (4.71)	
Comorbidities				
Diabetes mellitus type I	4 (1.48)	0 (0)	4 (2.09)	0.325§
Gestational diabetes	0 (0)	0 (0)	0 (0)	-
Hypertension	178 (65.93)	61 (77.22)	117 (61.26)	0.012†
Dyslipidemia	94 (34.94)	31 (39.24)	63 (33.16)	0.341†
Kidney disease	13 (4.81)	6 (7.59)	7 (3.66)	0.211§
Stroke or MI	43 (15.99)	17 (21.52)	26 (13.68)	0.110†
Thyroid disease	23 (8.52)	10 (12.66)	13 (6.81)	0.117†
Hypothalamic disease	0 (0)	0 (0)	0 (0)	-
Liver disease	4 (1.48)	1 (1.27)	3 (1.57)	0.999§
Inflammatory disease	4 (1.48)	3 (3.8)	1 (0.52)	0.077§
Neoplastic disease	5 (1.85)	3 (3.8)	2 (1.05)	0.151§
Others	47 (17.41)	19 (24.05)	28 (14.66)	0.064†
Years since DM diagnosis				0.452§
0–<1	52 (19.26)	11 (13.92)	41 (21.47)	
1–10	163 (60.37)	52 (65.82)	111 (58.12)	
11–20	38 (14.07)	10 (12.66)	28 (14.66)	
>20	7 (2.59)	1 (1.27)	6 (3.14)	
Unrecalled	10 (3.7)	5 (6.33)	5 (2.62)	

Statistical tests used: * - Independent t-test; † - Chi-square test; ‡ - Mann-Whitney U test; § - Fisher's exact test.

Table 2. Laboratory profile of patients with diabetes mellitus

	All (n=270)	HbA1c <7% (n=79)	HbA1c ≥7% (n=191)	*p*
	Median (Range); Frequency (%)			
25(OH)D, ng/mL	18.92 (3.56–56.3)	21.6 (5.56–56.3)	18.04 (3.56–36.4)	<0.001
Deficient (<20)	155 (57.41)	32 (40.51)	123 (64.4)	
Insufficient (20–30)	89 (32.96)	33 (41.77)	56 (29.32)	
Sufficient (>30)	26 (9.63)	14 (17.72)	12 (6.28)	
Total cholesterol, mg/dL	179.58 (75.79–516.88); [n=246]	159.67 (75.79–346.01); [n=66]	189.05 (81.19–516.88); [n=180]	0.001
HDL-C, mg/dL	40.59 (5.8–86.99); [n=246]	44.46 (14.46–73.07); [n=66]	38.47 (5.8–86.99); [n=180]	0.001
LDL-C, mg/dL	119.07 (22.42–298.04); [n=245]	92.37 (25.2–298.04); [n=66]	125.65 (22.42–272.92); [n=179]	0.005
Triglyceride, mg/dL	126.56 (23.01–790.31); [n=248]	100.45 (40.7–384.09); [n=66]	140.72 (23.01–790.31); [n=181]	<0.001
FPG, mg/dL	154.16 (12.52–366)	122 (37–263.09)	185.97 (12.52–366)	<0.001
HbA1c, %	8.71 (4.83–20.55)	6.17 (4.83–6.99)	10.16 (7–20.55)	-

Statistical test used: Mann-Whitney U test.

to have an HbA1c ≥7%. However, this association was no longer significant after adjusting for covariates (Table 4).

Using vitamin D as a continuous scale, this study found that patients with low vitamin D were 5.2 times less likely to have elevated FPG levels (crude OR 0.947, 95% CI 0.91 to 0.98, *p*=0.001). However, there was no association between vitamin D status and glycemic control after adjusting for covariates. Meanwhile, serum total cholesterol was found to be associated with elevated FPG even after adjusting for covariates (adjusted OR 1.011, 95% CI 1.005 to 1.02, *p*<0.001) (Table 5).

Table 3. Correlations of serum 25(OH)D with other patient factors

	25(OH)D (ng/mL)	
	Rho	*p*
Age, years	0.3386	<0.001
BMI, kg/m^2 [n=267]	-0.1343	0.028
Years since DM diagnosis [n=260]	0.1473	0.018
HbA1c, %	-0.2607	<0.001
FPG, mg/dL	-0.1983	0.001

DISCUSSION

The role of inflammation in the pathogenesis of diabetes mellitus and its associated metabolic disorders has been an emerging interest in its management.[16] The relationship between vitamin D levels and insulin resistance can be realized at the level of immunomodulatory processes and systemic inflammation, influencing the autoimmune pathology in type 1 diabetes and the low-grade chronic inflammation in type 2 diabetes.[6] The vitamin D receptors are expressed in different tissues, such as the adipose,

Table 4. Logistic regression analysis of the variables with HbA1c

	HbA1c ≥7%	*p*	HbA1c ≥7%	*p*
	Crude OR (95% CI)		Adjusted** OR (95% CI)	
Vitamin D, ng/mL	0.919 (0.88 to 0.95)	<0.001	-	
Vitamin D status				
Deficient	4.484 (1.89 to 10.64)	0.001	2.644 (0.94 to 7.47)	0.067
Insufficient	1.980 (0.82 to 4.79)	0.129	1.453 (0.50 to 4.21)	0.491
Sufficient	Reference (1.0)	-	Reference	-
Age	0.951 (0.93 to 0.97)	<0.001	0.952 (0.93 to 0.97)	<0.001
Male sex	1.351 (0.79 to 2.30)	0.269		
BMI	1.025 (0.99 to 1.07)	0.220		
Hypertension	0.467 (0.26 to 0.85)	0.013		
Smoking history				
No	Reference (1.0)	-	Reference (1.0)	-
Current	0.859 (0.39 to 1.89)	0.707	0.306 (0.12 to 0.77)	0.011
Former	1.355 (0.67 to 2.73)	0.394		
Alcohol drinker				
No	Reference (1.0)	-		
Current	1.037 (0.58 to 1.86)	0.902		
Previous	0.740 (0.24 to 2.32)	0.605		
Total cholesterol, mg/dL	1.008 (1.002 to 1.01)	0.004	1.006 (1.0001 to 1.01)	0.045
Adjusted R^2	-		14.84%	

**Vitamin D as a categorical predictor was forced into the final model using STATA lockterm 1 function

Table 5. Logistic regression analysis of the variables with FPG

	FPG ≥126 mg/dL	*p*	FPG ≥126 mg/dL	*p*
	Crude OR (95% CI)		Adjusted** OR (95% CI)	
Vitamin D, ng/mL	0.947 (0.91 to 0.98)	<0.001		
Vitamin D status				
Deficient	1.815 (0.74 to 4.43)	0.190	1.206 (0.42 to 3.50)	0.731
Insufficient	0.817 (0.33 to 2.04)	0.664	0.496 (0.17 to 1.49)	0.210
Sufficient	Reference (1.0)	-	Reference (1.0)	-
Age	0.977 (0.96 to 0.99)	0.008		
Male sex	0.938 (0.55 to 1.59)	0.811		
BMI	1.019 (0.98 to 1.06)	0.359		
Hypertension	0.612 (0.34 to 1.09)	0.096		
Smoking history				
No	Reference (1.0)	-		
Current	0.695 (0.32 to 1.51)	0.359		
Former	1.032 (0.52 to 2.03)	0.927		
Alcohol drinker				
No	Reference (1.0)	-		
Current	0.924 (0.52 to 1.65)	0.788		
Previous	0.519 (0.17 to 1.57)	0.246		
Total cholesterol, mg/dL	1.011 (1.005 to 1.02)	<0.001	1.011 (1.005 to 1.02)	<0.001
Adjusted R^2			8.26%	

**Vitamin D was analyzed as a categorical predictor

skeletal muscles, and pancreatic β-cells. Vitamin D has a pivotal role in regulating insulin secretion, insulin signaling, and improving insulin resistance.[3,4]

This study showed that vitamin D level is significantly but weakly correlated with the patient's age (ϱ=0.339) and duration of diabetes (ϱ=0.147), whereas it had inverse correlations with BMI (ϱ=-0.134), HbA1c (ϱ=-0.261), and FPG (ϱ=-0.198) (Table 3).

All participants were admitted and were assumed to have an acute illness; hence, some patients were expected to have higher FPG. Nevertheless, the median FPG was still significantly higher among vitamin D deficient (173.71 mg/dL) than among the insufficient (141.46 mg/dL) patients. On the other hand, HbA1c is a good clinical indicator since it reflects 2-3 months of glucose control.

In the study of Aalkhatatbeh et al., correlation analysis showed significant inverse correlations between 25(OH) D levels and HbA1c and FPG levels (r= 0.23 and 0.17, respectively, both $p<0.01$).[2] Multiple linear regression analysis revealed a significant inverse association between HbA1c and 25(OH)D levels (F=12.95, R2=0.48, $p<0.01$).[2]

Buhary et al., also detected a significant inverse association between HbA1c and 25(OH)D and observed that supplementation of vitamin D improved glycemic control by reducing HbA1c levels.[4] Ghavam et al., supports the findings of this study wherein an inverse linear relationship exists between 25(OH)D and HbA1c ($p<0.37$) and FPG ($p<0.64$).[12] The inverse correlation observed in this study for vitamin D and HbA1c in type 2 diabetic patients is similar to the findings of Salih et al., who showed that 25(OH)D level was significantly lower ($p<0.001$) for patients with poor glycemic control.[17]

As parameters for glucose control, elevated HbA1c and FPG may reflect greater insulin resistance and systemic inflammation. As part of its anti-inflammatory and immunomodulatory effects, vitamin D can influence glucose metabolism through its regulation of insulin secretion and signaling. Vitamin D deficiency can reduce intracellular calcium regulation of the expression of the insulin receptor, insulin signaling, and secretion, thereby affecting glucose levels.[18]

Our findings showed that the serum 25(OH)D level is significantly but weakly correlated with the patient's age (ϱ=0.339). Analysis by HbA1c indicated that those with poorer glycemic control were younger (mean: 53 vs. 64 years) even after adjusting for covariates, which may have influenced the levels of vitamin D in the study population. Findings were similar to Buhary et al., who found that older patients had higher vitamin D levels ($p=0.0001$).[4] Salih et al., and Yilmaz et al., did not demonstrate any significant association between age and vitamin D levels.[17,19] Salih et al., discussed that age is likely to negatively correlate with vitamin D since its production by sunlight in less efficient in older individuals. According to Gallagher, aging affects the metabolism of vitamin D and calcium through the following mechanisms: malabsorption of calcium; intestinal resistance of calcium absorption to circulating $1,25(OH)_2D$; decreased vitamin D receptors; impaired renal production of $1,25(OH)_2D$ with the age-related decline in kidney function; and reduced skin production of vitamin D.[20]

In this study, BMI was seen to decrease with more sufficient vitamin D levels, and this difference was significant. The median values of BMI in kg/m^2 were 27.55, 26.71, and 24.58 in the vitamin D deficient, insufficient, and sufficient groups, respectively. Ghavam et al., found an inverse linear relationship between vitamin D and BMI ($p<0.59$).[12] Similarly, the findings conducted by Sahli et al., showed that BMI had a highly significant effect ($p<0.001$) on vitamin D levels among patients with diabetes.[17]

Obesity has been identified as a known risk factor for vitamin D deficiency. A consequence of obesity is the impaired secretion of adipokines and systemic inflammation, which contributes to greater insulin resistance.[6,17] Higher vitamin D levels are accompanied by lower inflammatory markers, including tumor necrosis factor-α, interleukin-6, and C-reactive protein in those with inflammatory-associated diseases such as diabetes.[6] In obesity, there is increased storage of fat-soluble vitamin D in the adipose tissue and in the liver, which impairs the modulatory effects on the vitamin D receptors.[17,21,22] Obese patients are also at risk for a sedentary lifestyle which contributes to their inadequate sunlight exposure and lesser physical activity, thereby decreasing the conversion to the active form of vitamin D, $1,25(OH)_2D$.

Our findings showed a significant but weak negative correlation between the duration of diabetes (ϱ=-0.140) and 25(OH)D (ϱ=-0.198). Sahli et al., showed a significant difference between 25(OH)D levels of patients with a diabetes duration of >5 years and those with diabetes duration <5 years ($p=0.002$).[17] Ghavam et al., indicated no significant relationship between the duration of diabetes and vitamin D ($p<0.1$, r= 0.164).[12]

The retrospective nature of this investigation does not provide further insight. An area of future analysis is whether vitamin D supplementation will improve glycemic control and reduce the risk of the development of diabetes.

The anti-inflammatory and immunomodulatory effects of vitamin D may be modified by cigarette smoke since it contains harmful chemicals.[23,24] Cigarette smoking can also lower the production of the active form of vitamin D and may affect the expression of its vitamin D receptor.[23,24] Our findings showed that smoking was associated with elevated HbA1c levels, even after adjusting for covariates. Salih et al., showed that 25-hydroxyvitamin D levels are lower in smokers though the difference was not significant.[17] On the other hand, Hermann et al., showed that serum vitamin

D levels and osteocalcin were inversely related to the number of cigarettes smoked per day (r=0.11 and p<0.001; r=0.17 and p=0.04, respectively).[25]

Patients with hypovitaminosis D were younger, had higher BMI, HbA1c, and FPG levels. Adjusted associations revealed that HbA1c was progressively lower with more sufficient vitamin D levels, and the median FPG was significantly higher among vitamin D deficient patients. Our study suggests that the serum 25(OH)D levels may influence glucose homeostasis of patients with diabetes mellitus. This study supports the emerging role of vitamin D in metabolic dysregulation, pancreatic β-cell function, and inflammation in diabetes. Upreti et al., showed that oral vitamin D supplementation was associated with improved glycemic control and other metabolic parameters in diabetes mellitus.[26] However, a meta-analysis showed insufficient evidence of a beneficial effect to recommend vitamin D supplementation to improve glycemic control in patients with type 2 diabetes.[17] Further investigations are needed to validate these findings.

Limitations and recommendations of the study

Since the participants were not randomly sampled, an inherent selection bias is present in this study. Being primarily a retrospective review, confounding variables such as diet, physical activity, lifestyle, and sunlight exposure were not investigated. The authors suggest a research endeavor where additional data can be collected using interviews to document sunlight exposure, physical activity, and dietary habits.

The investigators recommend recruiting healthy patients from the outpatient clinics since the acute illness of admitted patients may have affected their metabolic state and glucose homeostasis. Another future research endeavor is to determine whether vitamin D supplementation can improve insulin sensitivity and affect glucose homeostasis. This may elucidate a causal relationship between vitamin D status, metabolic syndrome, and the microvascular and macrovascular complications of diabetes.

CONCLUSION

Our results demonstrated a weak inverse correlation between vitamin D levels and FPG and HbA1c levels. Vitamin D was also seen to be crudely associated with glycemic control, but such an association was not sustained after adjusting for covariates.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
ME: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition. **MJI:** Conceptualization, Validation, Writing – review and editing, Supervision, Funding acquisition. **NSAG:** Conceptualization, Validation, Writing – review and editing, Supervision, Project administration, Funding acquisition.

Author Disclosure
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