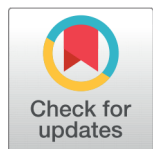


The correlation of vitamin D with HOMA-IR and glycated hemoglobin in type 2 diabetes mellitus patients

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ABSTRACT

Background and objective: Vitamin D's primary functions are the homeostasis of calcium and bone metabolism, but it also has a significant role in the homeostasis of plasma glucose. This study sought to examine the relationship between vitamin D and glycated hemoglobin and insulin resistance in type 2 diabetes mellitus (T2DM). **Methods:** A total of 150 patients with newly diagnosed T2DM participated in this case-control study. Additionally, 150 controls of the same age and gender were also recruited. Serum vitamin D and fasting insulin levels were estimated by the electrochemiluminescence immunoassay (ECLIA) method. And, high-performance liquid chromatography (HPLC) was used to analyze HbA_{1c}. Pearson's correlation coefficient was used to determine the association of vitamin D with HbA_{1c} and HOMA-IR.

Results: About 71% of diabetes patients had low vitamin D levels, compared to 31% in the control group. Vitamin D-deficient T2DM subjects had significantly higher HOMA-IR and HbA_{1c} levels. In addition, a strong negative association between vitamin D and HOMA-IR ($r = -0.75$) and vitamin D and HbA_{1c} ($r = -0.73$) has been demonstrated among T2DM patients.

Conclusions: Vitamin D deficiency is correlated with ineffective glycemic control, and the reason might be its potential role in the secretion and sensitivity of insulin. Therefore, vitamin D screening must be incorporated as a routine check-up for T2DM patients.

Keywords HOMA-IR, HbA_{1c}, type 2 diabetes mellitus, vitamin D

INTRODUCTION

Diabetes mellitus is one of the most prevalent endocrine conditions and is marked by an elevated level of plasma glucose. Type 2 diabetes (T2DM), which accounts for over 90% of all instances of diabetes, is caused by a reduced responsiveness of target cells to insulin (insulin resistance).¹ This is initially compensated by an increase in insulin production to

maintain normal glucose levels in the blood. But as the disease progresses, insulin production from pancreatic beta cells gradually decreases, and there is ultimately not enough of it to counteract the resistance, which leads to persistent hyperglycemia.¹

Chronic hyperglycemia in diabetic patients results in long-term micro and macrovascular complications. To prevent these complications, diabetic patients should maintain good glycemic status, which is routinely determined by measuring glycated hemoglobin, that is, hemoglobin A1c (HbA_{1c}). HbA_{1c} measures the average plasma glucose level during the previous two to three months.^{1,2} Insulin resistance, the hallmark of T2DM, can be assessed by different methods. The criterion standard technique for direct measurement of insulin resistance, the hyperinsulinemic-euglycemic glucose clamp method, has certain limitations as it requires a steady infusion of insulin and frequent blood collection, making it difficult for assessing large study participants.³ On the other hand, the homeostasis model assessment of insulin resistance (HOMA-IR) provides a quick and affordable way to estimate insulin resistance, as well as the assessment results have been demonstrated to be on par with the gold standard approach.⁴

Vitamin D, produced by the body or obtained through diet, is stored in adipose tissue as cholecalciferol (vitamin D₃). The main form of vitamin D that circulates in the body is 25-hydroxy vitamin D₃ [25(OH)D₃], also termed calcidiol, and it is mostly bound to the plasma protein vitamin D binding protein (VDBP). The metabolically dynamic form of vitamin D is 1,25-hydroxy vit. D₃ [1,25(OH)₂D₃], also termed calcitriol. Despite the fact that 1,25(OH)₂D₃ is the dynamic form of vitamin D, 25(OH)D₃ has a long half-life in the blood and is therefore considered to be the best marker for determining vitamin D level.⁵

Vitamin D receptors (VDRs) are found in a wide range of cell types, and vitamin D functions primarily through VDRs in the homeostasis of calcium and the metabolism of bone.⁶ Pancreatic beta cells also contain VDRs, and vitamin D binds to these VDRs, resulting in glucose-stimulated secretion of insulin.⁷ Additionally, vitamin D affects VDRs, which in turn influences insulin receptor expression in adipose tissue and skeletal muscle. This enhances insulin sensitivity in these cells, resulting in prompt uptake and utilization of glucose in response to insulin secretion.^{8–10} Therefore, it is postulated that vitamin D actively contributes to glucose homeostasis. Consequently, one of the pathophysiological reasons for T2DM may be attributed to vitamin D deficiency.¹¹ But only limited studies have explored the interaction of 25(OH)D₃ with insulin resistance, especially in people with recently diagnosed type 2 diabetes and those living in rural regions. The purpose of the current study was to investigate the relationship of vitamin D with insulin resistance and glycated haemoglobin in type 2 diabetics.

MATERIALS AND METHODS

Subjects and research design

The research was done using a case-control research design at a rural tertiary level care center over the course of twelve (12) months, from August 2021 to August 2022. The study's

premise was approved by the Institutional Ethics Committee, and each participant provided informed consent. The complete medical history of each participant was obtained, and they were screened based on the inclusion and exclusion criteria. The criteria for inclusion were: diagnosed cases of T2DM (case group) of not more than 6 months duration; taking regular medication only in the form of oral hypoglycemic medicines; and being between the ages of 30 and 70 years. Age- and gender-matched healthy euglycemic individuals as controls.

Any participants with the following diseases were excluded: T2DM with micro and macrovascular complications, type 1 diabetes mellitus, chronic kidney/liver/pancreatic diseases, thyroid/parathyroid/bone disorders, hypertension/dyslipidemia/smoking/alcoholism, a history of myocardial infarction, angina and stroke. Pregnant women, patients with any other endocrinopathies, and patients using medications and supplements (e.g., insulin, corticosteroids, anticonvulsants, contraceptives, vitamin D, and calcium) were also excluded from the study. We chose 300 participants based on the inclusion and exclusion criteria. Of these, 150 recently diagnosed T2DM patients were considered cases. As controls, 150 additional age- and gender-concordant healthy adults were enrolled. Based on their vitamin D levels in the blood, the case subjects were divided into three groups: Group 1 is a deficiency (20 ng/ml or less); insufficiency (20-29 ng/ml) is in Group 2; and Group 3 is normal (30 ng/ml or higher).

A detailed clinical history was recorded, anthropometric (height and weight) and blood pressure measurements (systolic and diastolic pressure) were performed. Body mass index (BMI) was computed for each study participant using the following formula:

$$BMI = \left(\frac{Weight (kg)}{(Height (m))^2} \right)$$

Participants were deemed obese if their BMI exceeded 30.0 kg/m².

Biochemical analyses

All enrolled individuals had their venous blood drawn under stringent aseptic guidelines. For the purpose of determining fasting plasma glucose and insulin, overnight fasting venous blood was collected. Within an hour after blood collection, it was centrifuged for 10 minutes at 3000 rpm to separate the serum. Prior to the test runs, the samples were kept refrigerated at a temperature of -20°C. HbA_{1c} was determined using whole blood samples, and glucose was determined using plasma. The glucose oxidase peroxidase (GOD-POD) method was used to estimate plasma glucose. The high-performance liquid chromatography (HPLC) technique was applied to measure HbA_{1c}. The electrochemiluminescence immunoassay (ECLIA) method was used to measure 25-hydroxy vitamin D₃ and fasting insulin concentrations. Using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula, the insulin resistance was determined (for SI units)¹². The formula

is:

$$HOMA - IR = \left(\frac{Fasting\ glucose\ (mg/dl) \times Fasting\ insulin\ (IU/ml)}{405} \right)$$

Patients whose HOMA-IR score was greater than 2.5 were considered to have insulin resistance.¹³

Statistical analysis

The statistical analysis was performed utilizing Windows version 20.0 of the Statistical Package for Social Survey (SPSS). The mean and the standard deviation (SD) for all the baseline variables were calculated. The student t-test (unpaired) and Mann Whitney U test were used to compare variables as appropriate. Categorical variables were computed using the chi-square test. Karl Pearson's correlation coefficient was used to ascertain the correlation of vitamin D with HbA_{1c} and HOMA-IR. Statistical significance was defined as a "p value <0.05", and a "p value <0.001" was regarded as highly significant.

RESULTS

There were 300 subjects enrolled in the current study, 150 of whom had T2DM (case group) and another 150 were healthy euglycemic individuals (control group). The subjects were all between the ages of 30 and 70 years. Table 1 compares baseline characteristics between cases and controls.

Table 1 Comparison of baseline characteristics between cases and controls.

Parameters	Cases (n=150)	Control (n=150)	P value
Age (years)	52.41±7.36	51.54±7.51	0.31
Gender (male/female)	96/54	95/55	0.90
Fasting plasma glucose (mg/dl)	116.88±17.36	92.98±4.05	<0.001
Post prandial plasma glucose (mg/dl)	190.15±27.43	119.67±8.63	<0.001
Body Mass Index (Kg/m ²)	23.12±1.21	22.89±1.09	0.08
Systolic blood pressure (mm Hg)	118.87±5.37	117.97±4.56	0.12
Diastolic blood pressure (mm Hg)	78.05±5.20	77.12±4.53	0.10

All values have been elaborated as mean±SD, except gender; standard deviation (SD); *p*<0.05 significant, *p*<0.001 highly significant.

The case group's mean age was 52.41±7.36 years, while the control group's mean age was 51.54±7.51 years. Out of 150 T2DM patients, 96 were males and 54 were females. In our present study, male predominance (64% vs. 36%) was noted among diabetes mellitus patients. Because matched controls were selected, there was no obvious difference in age or gender between the case and control groups (*p*> 0.05). Figure 1 shows the gender distribution in percentages in the study groups.

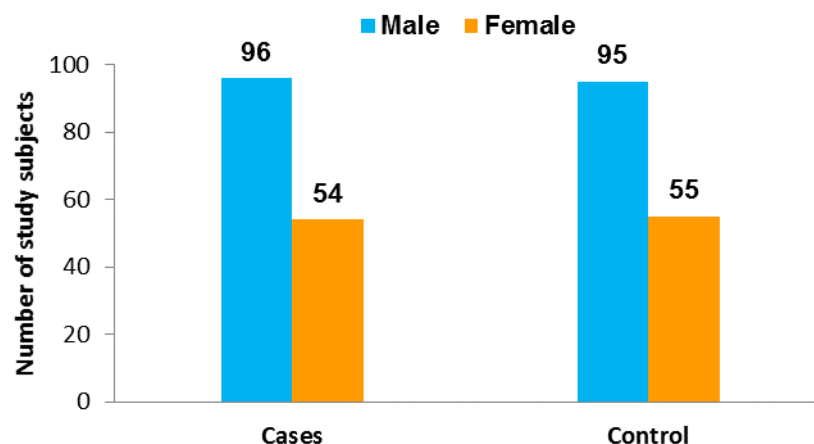


Figure 1 Gender distribution in percentages in the study groups

Fasting plasma glucose and postprandial plasma glucose levels differed significantly ($p<0.001$) between cases and controls. The case group mean BMI was found to be 23.12 ± 1.21 kg/m², while the control group was 22.89 ± 1.09 kg/m², with no significant difference between the two groups ($p=0.08$). There were no statistically significant differences in systolic ($p=0.12$) or diastolic ($p=0.10$) blood pressure between the cases and the controls. Among T2DM subjects, 72 (48%) had deficient vitamin D levels, 34 (22.7%) had insufficient vitamin D levels, and 44 (29.3%) had normal vitamin D levels. Among controls, 47 (31.3%) had low vitamin D levels, while 103 (68.7%) had normal vitamin D levels. Table 2 lists the biochemical characteristics of the case and control groups.

Table 2 Biochemical characteristics of the cases and control groups.

Parameters	Cases (n=150)			Control (n=150)
	Group 1 (n=72)	Group 2 (n=34)	Group 3 (n=44)	
Vitamin D (ng/ml)	15.54 ± 2.64	24.20 ± 2.75	34.98 ± 3.01	33.84 ± 6.57
HbA _{1c} (%)	7.94 ± 0.86	7.46 ± 0.78	6.31 ± 0.55	5.35 ± 0.18
Fasting Insulin (μ IU/ml)	9.13 ± 1.25	8.64 ± 0.98	7.81 ± 0.58	7.92 ± 0.57
HOMA-IR	2.88 ± 0.48	2.61 ± 0.37	1.87 ± 0.19	1.83 ± 0.14

*SD: Standard deviation; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HbA_{1c}: Haemoglobin A_{1c} (glycated haemoglobin).

When case groups were compared among themselves (group-1 vs. group-2, group-1 vs. group-3 and group-2 vs. group-3) and with controls (group-1 vs. control, group-2 vs. control and group-3 vs. control), statistically distinct differences ($p<0.001$) existed in vitamin D levels, with the exception of group-3 and controls ($p=0.11$). Statistically significant differences existed in HbA_{1c} levels ($p<0.01$) when case groups were compared among each other and also with control. Similarly when case groups were compared to one another as well as with controls, fasting insulin levels varied significantly, with the exception of group-

3 and control ($p=0.24$). Statistically significant differences existed in HOMA-IR ($p<0.01$) when case groups were compared among each other and also with control, except between group-3 and control ($p=0.07$). Figure 2 (A, B) compares the levels of serum vitamin D and HbA_{1c}, whereas Figure 3 (A, B) compares the levels of serum fasting insulin and HOMA-IR levels in case groups and controls.

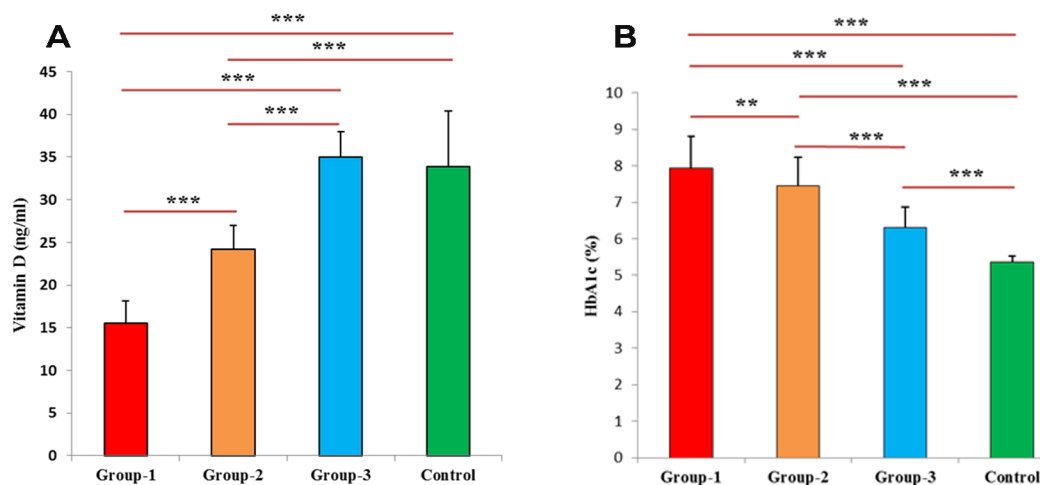


Figure 2 Comparison of serum vitamin D and HbA_{1c} levels in case groups and controls. A) Serum vitamin D levels. B) HbA_{1c} levels (hemoglobin A_{1c}). *** denotes $p<0.001$. ** denotes $p<0.01$.

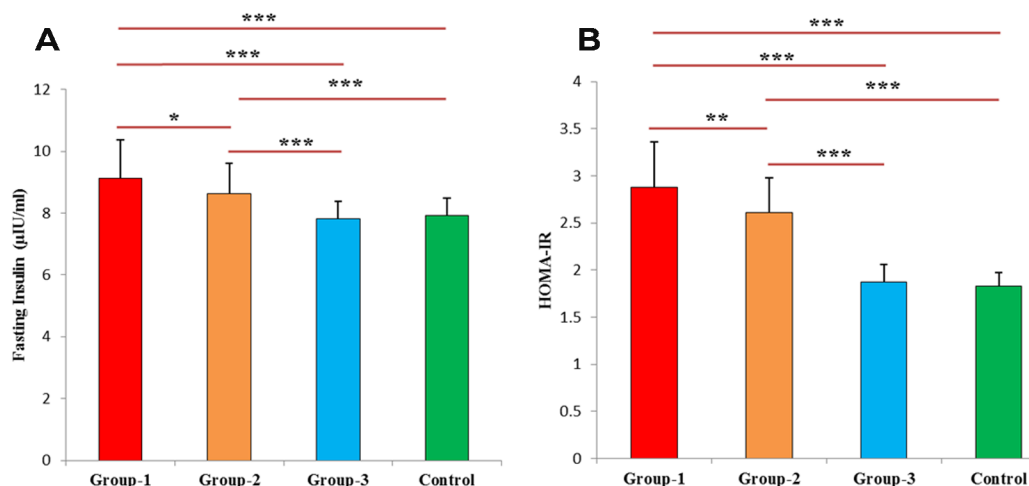


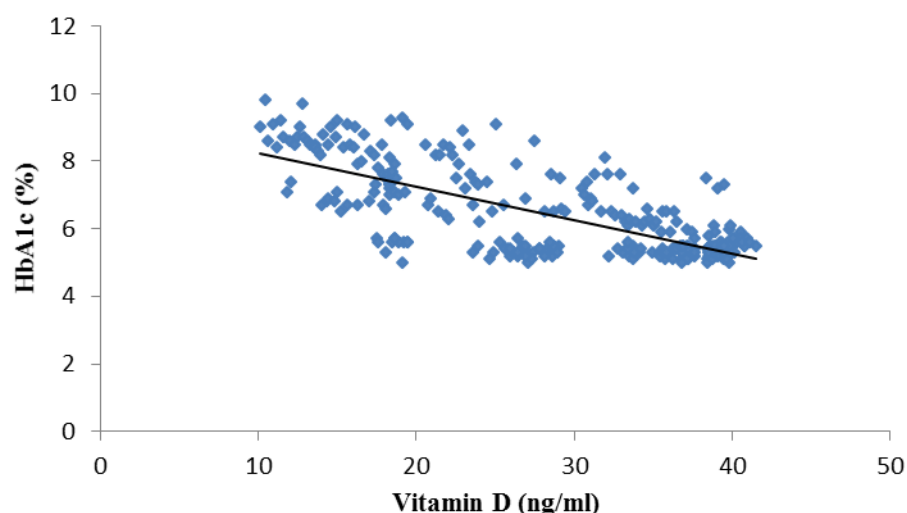
Figure 3 Comparison of serum fasting insulin and HOMA-IR levels in case groups and controls. A) Serum fasting insulin levels. B) HOMA-IR (homeostasis Model Assessment of Insulin Resistance levels). *** denotes $p<0.001$. ** denotes $p<0.01$. * denotes $p<0.05$.

In study participants, the Pearson's correlation coefficient revealed a statistically significant inverse correlation ($r = -0.73$) between vitamin D and HbA_{1c} levels. Table 3 demonstrates the correlation strength of HbA_{1c} and HOMA-IR with vitamin D.

Table 3 Correlation between HbA_{1c} and HOMA-IR with vitamin D.

Parameters	Vitamin D	
	r	p
HbA _{1c}	-0.73	<0.001
HOMA-IR	-0.75	<0.001

An inverse correlation ($r = -0.75$) was also observed between HOMA-IR and vitamin D levels in study participants by Pearson's correlation coefficient, which was statistically significant. Figure 4 scatter plot portrays the relationship between HbA_{1c} and Vitamin D, whereas Figure 5 scatter plot portrays the relationship between HOMA-IR and vitamin D.

**Figure 4** Scatter plot demonstrating the relationship between HbA_{1c} and vitamin D.

DISCUSSION

The goal of the current study was to assess how vitamin D affects glycemic control and insulin resistance in T2DM patients. Although maintaining calcium homeostasis is the primary role of vitamin D, this steroid hormone also has a wide range of additional functions.⁶⁻⁸ It is crucial in research to investigate how vitamin D affects insulin sensitivity and plasma glucose levels in order to better understand how it impacts glycemic management. The majority of the cases in our study belong to the age group of 50–60 years. The study also showed male predominance among T2DM patients. The research directed by Aregbesola A et al.¹⁴ observed a high prevalence of T2DM in males. There was a substantial difference in fasting and postprandial glycemic state between the case and control groups. However,

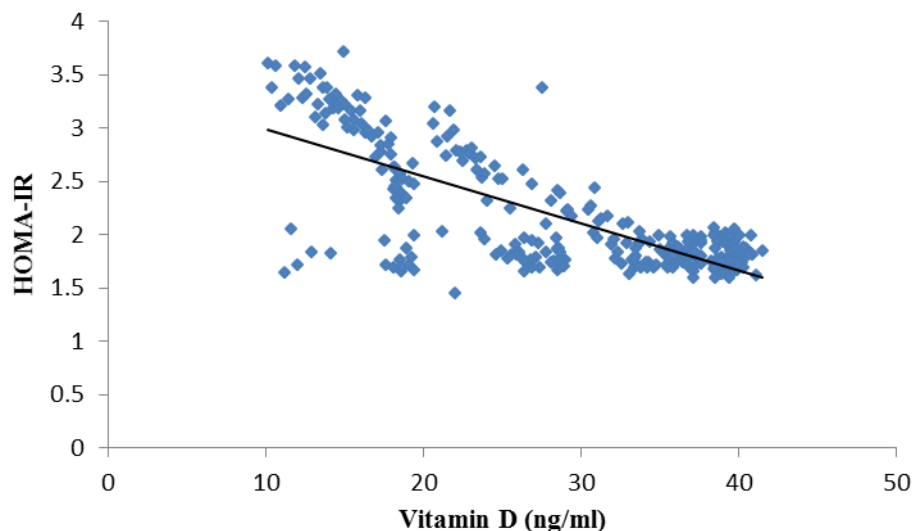


Figure 5 Scatter plot demonstrating the relationship between HOMA-IR and vitamin D.

while confounding factors like obesity and hypertension, which may potentially affect vitamin D levels, were excluded when cases were chosen, there was no statistically noteworthy difference in BMI and blood pressure between the cases and healthy control subjects. Excessive fat deposition and dyslipidemia may lower vitamin D levels and activity in adipose tissue, which may skew the association between vitamin D and insulin resistance.¹⁵

According to the current study, vitamin D deficiency is more common in diabetic patients, with 70.7% of diabetes subjects having reduced vitamin D levels compared to 31.3% in the control groups. The study done by Kostoglou-Athanassiou et al.¹⁶ showed that vitamin D deficiency was more common in diabetic patients, with 80.8% (17.5% and 63.3% vitamin D deficiency and insufficiency, respectively) of diabetic subjects having low vitamin D levels compared to 29.1% (5.8% and 23.3% vitamin D deficiency and insufficiency, respectively) in the healthy control groups. Additionally, compared to controls, vitamin D levels in T2DM patients were considerably lower in our study. In their study, Bayani et al.¹⁷ reported that T2DM patients had low levels of vitamin D as compared to healthy controls.

In order to ascertain how vitamin D affects glycemic status, the current study sought to examine the association between vitamin D and glycated haemoglobin (HbA_{1c}) and insulin resistance in both diabetic and healthy subjects. The results of this study showed that diabetic individuals with low vitamin D levels had substantially higher HbA_{1c} values than patients with adequate vitamin D status. In addition, vitamin D levels and glycemic control, as determined by HbA_{1c}, showed a statistically significant inverse association. The higher HbA_{1c} levels in T2DM subjects with vitamin D deficiency compared to their vitamin D sufficient counterparts are in line with past studies of a similar kind that revealed an inverse association between vitamin D levels and HbA_{1c} levels.^{16,18} However, the serum vitamin D levels and HbA_{1c} in diabetes individuals were not shown to be significantly correlated in

a study by Ghavam et al.¹⁹

In this investigation, we discovered that the mean HOMA-IR levels of diabetes patients with deficient or insufficient vitamin D levels were significantly higher than those of diabetic patients with adequate vitamin D levels. Additionally, and independently of confounding factors, there was a statistically noteworthy inverse correlation between serum vitamin D levels and HOMA-IR measurements of insulin resistance. Quite a few studies conducted by researchers have revealed a similar relationship between serum vitamin D levels and HOMA-IR in diabetic patients.^{20,21} The above observations infer that glycemic control as evaluated by HbA1c levels and insulin resistance as determined by HOMA-IR were greater in diabetic patients with a deficiency in vitamin D, implying a possible link between vitamin D and glucose homeostasis.

The influence of vitamin D on glucose homeostasis may be mediated through a variety of mechanisms, and its deficiency may naturally accentuate T2DM. Vitamin D receptors have been discovered in a number of organs, including the beta islet cells of pancreas, which produce insulin and are dependent on calcium. Binding of the circulating dynamic type of vitamin D [1,25(OH)D₃] to these receptors generates an adequate calcium ion pool, which may result in increased pancreatic insulin production in response to high blood glucose levels.^{7,22} This suggests that vitamin D may play a noteworthy role in insulin secretion and, that its deficiency wane secretion of insulin from beta cells of pancreas in response to glucose.²³ Vitamin D is correspondingly crucial for insulin receptor expression in the liver, adipose tissues, and skeletal muscles. This increases the insulin receptors' sensitivity to insulin, which in turn increases glucose uptake.⁹

T2DM is characterised by low-grade inflammation caused by an increase in circulating cytokines such as tumour necrosis factor-alpha (TNF- α) and interleukins (IL), which worsens insulin resistance, particularly in muscles and adipose tissue.²⁴ The powerful anti-inflammatory and immune-modulatory properties of vitamin D tend to repress transcription of these pro-inflammatory cytokine genes, making vitamin D protective against insulin resistance.^{22,25} In brief, the development and progression of T2DM are attributed to insulin resistance, impaired function of pancreatic beta-cells, and systemic inflammation, and data indicates that vitamin D imbalance might be a contributing factor in the development and worsening of T2DM.^{7,26} Furthermore, some studies have shown that supplementing with vitamin D improves the glycemic state of diabetics.^{27,28} Therefore, all diabetic and pre-diabetic patients must be evaluated for vitamin D deficiency, and supplementation of vitamin D should be incorporated as a standard treatment procedure in order to prevent further deterioration of the diabetic state. However, more studies are warranted to evaluate the effectiveness of vitamin D supplementation in preventing diabetes, particularly in high-risk populations.

Several factors that can interfere with vitamin D and glycemic status, such as obesity, dyslipidemia, and so on, were excluded from the study, which reinforced our findings by eliminating the potential confounding effects. Our study's limitations include the single-center design; the use of HOMA-IR as a substitute for the gold standard test; and the inability to assess the impact of vitamin D supplementation on insulin resistance and glycemic status.

CONCLUSIONS

The current research revealed that vitamin D levels were inversely and independently correlated with insulin resistance and HbA_{1c} in type 2 diabetic patients. The deficiency of vitamin D is associated with poor glycemic control and the reason might be its potential role in insulin secretion and sensitivity. Therefore, our research suggests that diabetic patients should undergo routine vitamin D screening, and if insufficient levels are discovered, vitamin D supplementation should be taken into consideration as it may help to improve glycemic status.

ABBREVIATIONS

T2DM, Type 2 Diabetes Mellitus; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HbA_{1c}, Haemoglobin A_{1c}; 25(OH)D₃, 25-hydroxy Vitamin D₃; 1,25(OH)₂D₃, 1,25-dihydroxy Vitamin D₃; VDR, Vitamin D Receptor; BMI, Body Mass Index; GOD-POD method, Glucose Oxidase Peroxidase method; HPLC, High-Performance Liquid Chromatography; ECLIA, Electro Chemiluminescence Immunoassay; SD, Standard Deviation.

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None.

DECLARATIONS

Authors' contributions

Conceptualization, data curation, formal analysis, methodology, project administration, software, supervision, visualization, writing-original draft, writing-review, and editing: SKN. Investigation, resources, validation: SKN, RG. Funding acquisition: N/A. All authors discussed the results, reviewed and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

Ethical approvals

The study protocol was reviewed and approved by the Institutional Ethics Committee, vide approval letter no.164/Acad/SUTMS/2021, dated July 30, 2021. Informed verbal consent was obtained from all study participants.

Data availability

The data that support the findings of this study is available from the corresponding author, upon reasonable request.

Funding resources

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