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Diabetes & its Complications

# The Role of Vitamin D, in the Pathogenesis and Glycemic Control of Type 2 Diabetes Mellitus

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## Keywords
Vitamin D, Diabetes Mellitus, Pathogenesis, Type 2 diabetes.

## Introduction
Diabetes Mellitus is a disorder in which the body does not produce enough or respond normally to insulin, causing blood glucose levels to be abnormally high. The number of people living with diabetes rose from 200 million in 1990 to 830 million in 2022. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries [1]. Diabetes mellitus (DM) is a metabolic disorder characterized by abnormally high blood glucose levels. Diabetes mellitus is becoming a worldwide health issue. It is responsible for about 1 million deaths per year, making it the ninth most prominent cause of death [2] and the global prevalence of diabetes is expected to rise by 10.1% by 2030 [3]. There are many types of diabetes, and the most common types and that we will focus on in this study are type 2 diabetes. Type 2 diabetes accounts for more than 90%-95% of diabetes and is caused by a combination of insulin resistance and an insufficient compensatory insulin production response [4,5]. Vitamin D receptors are present in both pancreatic beta-cells and immune cells. Beside its classical role as the major regulator for calcium absorption, vitamin D mediates the activity of beta-cell calcium-dependent endopeptidases promotes conversion of proinsulin to insulin and increases insulin output. In peripheral insulin target tissues, vitamin D enhances insulin action via regulation of the calcium pool. Vitamin D also acts as a potent immunosuppressor. It tends to down-regulate the transcription of various proinflammatory cytokine genes like Interleukin-2, Interlukin-12 and Tumor Necrosis Factor-alpha. It promotes the induction of regulatory T-lymphocytes, the production of anti-inflammatory cytokines and protects beta-cell from destruction. Vitamin D deficiency predisposes probable for type 2 diabetes. Vitamin D deficiency impairs insulin secretion and induces glucose intolerance. Vitamin D related genes are associated with different pathogenetic traits of the disease. Vitamin D supplementation has shown to reduce the risk of developing type 1 diabetes. Vitamin D has also been shown to reduce the risk of diabetes associated complications [6]. To date, the link between diabetes and vitamin D has not been definitively determined.

Although important knowledge has been acquired on the etiology of diabetes its precise etiopathogenesis is still under discussion. Inflammatory factors, reactive oxygen species and autoimmune reactions have all strongly emerged as the major pathogenic effectors for diabetes. Recently, vitamin D has sparked widespread interest in the pathogenesis and prevention of diabetes. As the major regulator for calcium homeostasis, vitamin D directly and or indirectly improves insulin exocytosis via activating calcium-dependent endopeptidases. Vitamin D also improves glucose tolerance [7].

## Methods
The purpose of the study is whether there is a correlation between vitamin D levels and blood glucose levels. In an observational study, type 2 adult diabetes subjects have been analyzed for vitamin D levels. The primary aim of this study was to estimate vitamin D levels in diabetic patients, in relation to age, gender, duration of known diabetes, HbA1c levels, use of sweeteners and coffee. This study comprised of 149 diabetic patients adults of both genders observed during the years 2020-2021. The characteristics of the patients included in the study are presented in Table 1.

**Table 1:** Patients with diabetes type2 in the study.

| | | | | |
|---|---|---|---|---|
| Valid | 149 | 149 | 149 | 149 |
| Mean | 7.10 | 19.7614 | 63.21 | 8.0809 |
| Std. Deviation | 6.515 | 6.68919 | 9.937 | 1.68470 |
| Minimum | 0 | 6.60 | 25 | 4.90 |
| Maximum | 30 | 34.00 | 88 | 14.30 |

IBM SPSS Statistics version 26 software for Microsoft Windows was used throughout the statistical analysis. A p-value of $< 0.05$ was treated to be significant.

## Results

Males account for 66 (44.3%) of the cases. There are 73 (49.0%) cases with urban residence. Regarding age (Figure 1), the average age was 63.2 years (25 - 88 years), 42 (28.2%) patients were aged 60-64 years, and the majority of patients were in the 55-74 age group with 107 (71.8%) patients.

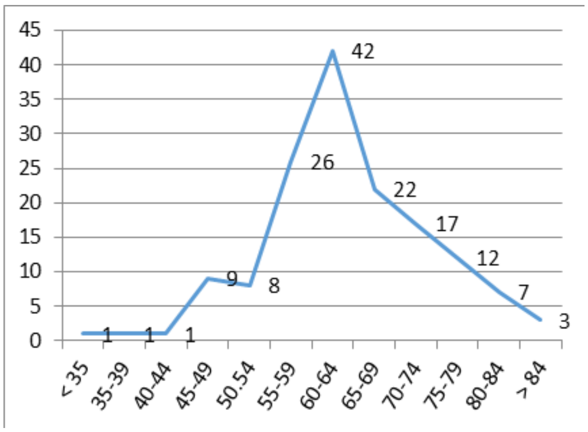


**Figure 1:** Age group of patients in the study with type 2 Diabetes mellitus.

The mean HbA1c levels (Figure 2) resulted in 8.08% (above the diabetic threshold of 6.5%) with a range of 4.9 - 14.3%. HbA1c in 41 (27.5%) of the patients resulted <7%, <8% in 40 (26.8%), 8-10% in 52 (34.9%) and >10% in 16 (10.7%).

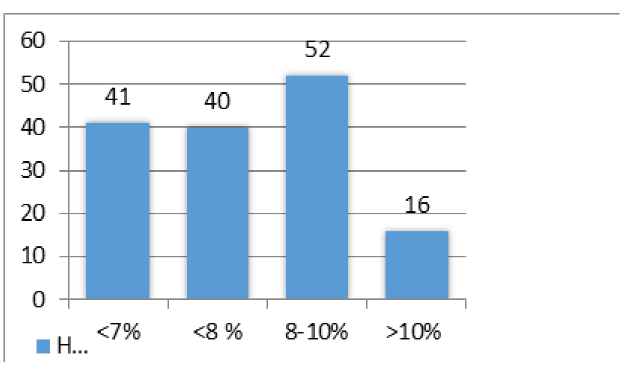


**Figure 2:** HbA1c levels in patients with diabetes type 2.

Vitamin D levels (Figure 3) in diabetic patients were: 30-70 ng/ml in 8 (5.4%), 10 – 30 ng/ml in 129 (86.6%) and <10 ng/ml in 12 (8.1%). The average vitamin D value resulted in 19.76 ng/mL (borderline deficiency) with a range of 6.6 - 34 ng/mL.

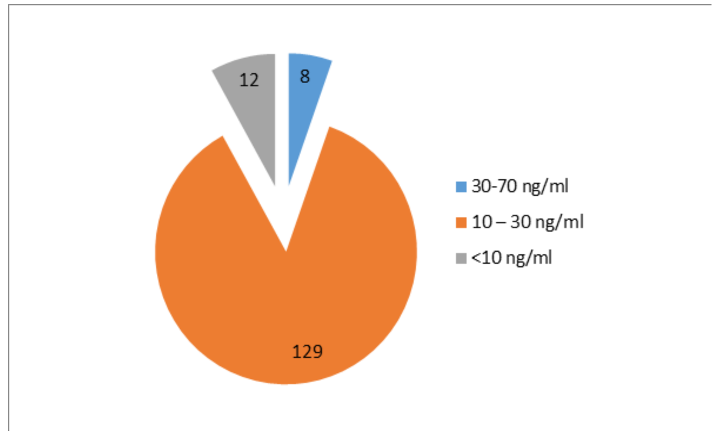


**Figure 3:** Levels of vitamin D in diabetic patients.

The duration of diabetes was on average 7.1 years, standard deviation 6.515 (from new diagnosis to 30 years). Newly diagnosed diabetes was present in 14 (9.4%) cases, < 2 years in 27 (18.1%), 2.1 -5 years in 38 (25.5%), 5.1 -10 years in 36 (24.2%), 10.1 - 15 years in 14 (9.4%) and >15 years in 20 (13.4%) of the cases. 56 (37.6%) patients used sweeteners. 119 (79.9%) patients were non-coffee drinkers, 11 (7.4%) consumed one cup of coffee per day, 2 on day 7 (4.7%), 3 on day 7 (4.7%) and 4 cups of coffee on day 5 (3.4) patients. Sweeteners were used by 56 (37.6%) of the patients.

Vitamin D by gender is presented in Table 2. There is no significant correlation between Vitamin D levels and gender. Males and females have similar distributions of Vitamin D levels.

**Table 2:** Vitamin D and Gender of patients with diabetes type 2.

| Vitamin D | Gender | | Total |
|---|---|---|---|
| | Males | Females | |
| 30-70 ng/ml | 3 | 5 | 8 |
| 10-30 ng/ml | 58 | 71 | 129 |
| >10 ng/ml | 5 | 7 | 12 |
| Total | 66 | 83 | 149 |

Pearson Chi-Square Value 0.207, Asymptotic Significance (2-sided) 0.902.

Vitamin D by Urban vs. Rural Residence presented in Table 3. There is no significant correlation between Vitamin D levels and place of residence. Vitamin D deficiency is present at similar rates in both urban and rural populations.

**Table 3:** Vitamin D and Urban vs. Rural Residence.

| Vitamin D | Residence | | Total |
|---|---|---|---|
| | Urban | Rural | |
| 30-70 ng/ml | 5 | 3 | 8 |
| 10-30 ng/ml | 63 | 66 | 129 |
| >10 ng/ml | 5 | 7 | 12 |
| Total | 73 | 76 | 149 |

Pearson Chi-Square Value 0.843, Asymptotic Significance (2-sided) 0.656.

There is a borderline correlation between age and Vitamin D levels ($p \approx 0.059$). Severe Vitamin D deficiency (<10 ng/ml) is more common in older age groups (>65 years). Younger groups have slightly better Vitamin D levels (Table 4).

**Table 4:** Age and Vitamin D Levels of patient with diabetes type 2.

| Age | Vitamin D | | | Total |
|---|---|---|---|---|
| | >30 ng/ml | 10-30 ng/ml | <10 ng/ml | |
| <35 | 0 | 1 | 0 | 1 |
| 35-39 | 0 | 1 | 0 | 1 |
| 40-44 | 0 | 1 | 0 | 1 |
| 45-49 | 1 | 7 | 1 | 9 |
| 50-54 | 0 | 8 | 0 | 8 |
| 55-59 | 0 | 25 | 1 | 26 |
| 60-64 | 3 | 39 | 0 | 42 |
| 65-69 | 1 | 19 | 2 | 22 |
| 70-74 | 2 | 14 | 1 | 17 |
| 75-79 | 1 | 8 | 3 | 12 |
| 80-84 | 0 | 5 | 2 | 7 |
| >84 | 0 | 1 | 2 | 3 |
| Total | 8 | 129 | 12 | 149 |

Pearson Chi-Square Value 33.179, Asymptotic Significance (2-sided) 0.059.

Results no significant correlation between age and HbA1c ($p > 0.05$). Glycemic control varies across different age groups, but no clear trend is seen (Table 5).

**Table 5:** Age and HbA1c of patients with diabetes type 2.

| Age | HbA1c | | | | Total |
|---|---|---|---|---|---|
| | <7% | <8 | 8-10 | >10 | |
| <35 | 0 | 1 | 0 | 0 | 1 |
| 35-39 | 0 | 1 | 0 | 0 | 1 |
| 40-44 | 1 | 0 | 0 | 0 | 1 |
| 45-49 | 2 | 5 | 2 | 0 | 9 |
| 50-54 | 0 | 2 | 4 | 2 | 8 |
| 55-59 | 10 | 4 | 10 | 2 | 26 |
| 60-64 | 14 | 11 | 15 | 2 | 42 |
| 65-69 | 5 | 7 | 8 | 2 | 22 |
| 70-74 | 4 | 5 | 4 | 4 | 17 |
| 75-79 | 3 | 2 | 5 | 2 | 12 |
| 80-84 | 1 | 1 | 3 | 2 | 7 |
| >84 | 1 | 1 | 1 | 0 | 3 |
| Total | 41 | 40 | 52 | 16 | 149 |

Pearson Chi-Square Value 29.542, Asymptotic Significance (2-sided) 0.640.

Most diabetic patients (129 out of 149) had Vitamin D levels in the 10-30 ng/ml range, which is considered insufficient. Only 8 patients had optimal Vitamin D levels. Considering Chi-Square Value = 20.670, p-value = 0.024, there is a significant correlation between diabetes duration and Vitamin D levels ($p < 0.05$) (Table 6).

**Table 6:** Vitamin D and Diabetes Duration of patients with diabetes type 2.

| Vitamin D | Years with Diabetes | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | Newly diagnosed | <2 | 2.1-5 | 5.1 -10 | 10.1 - 15 | >15 years | |
| 30-70 ng/ml | 1 | 0 | 5 | 0 | 1 | 1 | 8 |
| 10-30 ng/ml | 9 | 27 | 32 | 32 | 12 | 17 | 129 |
| <10 ng/ml | 4 | 0 | 1 | 4 | 1 | 2 | 12 |
| Total | 14 | 27 | 38 | 36 | 14 | 20 | 149 |

Pearson Chi-Square Value 20.670, Asymptotic Significance (2-sided) 0.024.

There is a strong significant correlation between Vitamin D levels and HbA1c levels. Patients with well-controlled diabetes (HbA1c <7%) had higher Vitamin D levels. Patients with poor glycemic control (HbA1c >10%) had lower Vitamin D levels. This suggests that Vitamin D deficiency might be linked to poor diabetes control (Table 7).

**Table 7:** Vitamin D and HBA1C (Glycemic Control) in patients with diabetes type 2.

| Vitamin D | HbA1c | | | | Total |
|---|---|---|---|---|---|
| | <7% | <8% | 6-10% | >10% | |
| 30-70 ng/ml | 5 | 3 | 0 | 0 | 8 |
| 10-30 ng/ml | 36 | 36 | 46 | 11 | 129 |
| <10 ng/ml | 0 | 1 | 6 | 5 | 12 |
| Total | 41 | 40 | 52 | 16 | 149 |

Pearson Chi-Square Value 24.525, Asymptotic Significance (2-sided) 0.000.

Bayesian Correlation of data studed are presented in (Table 8).

We analyzed the correlation between Vitamin D and HbA1c and Compare Vitamin D levels across different HbA1c groups. It resulted correlation Coefficient (r) = -0.439. This suggests a moderate negative correlation between Vitamin D levels and HbA1c. Higher Vitamin D levels are associated with lower HbA1c values.

## Discussion

Despite many studies showing a connection between vitamin D and diabetes, uncertainty of vitamin D's effects still exists. Vitamin D is believed to improve the body's sensitivity to insulin, which helps regulate blood sugar levels. This can reduce the risk of insulin resistance, a precursor to type 2 diabetes. People with type 2 diabetes often have lower levels of vitamin D.

Low vitamin D levels have been linked to high levels of inflammatory markers, impaired pancreatic beta-cell function, and insulin resistence [8-10].

In our study, vitamin D levels in most patients (129 out of 149) resulted in the 10-30 ng/ml range, which is considered insufficient. Only 8 patients had optimal Vitamin D levels. And from the literature data it has been found a significant association between vitamin D deficiency and type 1 and type 2 diabetes development

**Table 8:** Bayesian Correlation of data studed in patients with diabetes type 2.

| Data | Correlation Analysis | Vitamin D | Years with Diabetes | Sweetener use | Urban/rural residency | Gender | Age | HbA1c |
|---|---|---|---|---|---|---|---|---|
| Vitamin D | Pearson Correlation | 1 | -.100 | -.042 | .033 | -.014 | -.425** | -.439** |
| | Sig. (2-tailed) | | .225 | .611 | .689 | .869 | .000 | .000 |
| | N | 149 | 149 | 149 | 149 | 149 | 149 | 149 |
| Years with Diabetes | Pearson Correlation | -.100 | 1 | .042 | -.090 | .066 | .230** | -.049 |
| | Sig. (2-tailed) | .225 | | .612 | .274 | .425 | .005 | .549 |
| | N | 149 | 149 | 149 | 149 | 149 | 149 | 149 |
| Sweetener use | Pearson Correlation | -.042 | .042 | 1 | .099 | .089 | -.057 | -.056 |
| | Sig. (2-tailed) | .611 | .612 | | .231 | .280 | .487 | .497 |
| | N | 149 | 149 | 149 | 149 | 149 | 149 | 149 |
| Urban/rural residency | Pearson Correlation | .033 | -.090 | .099 | 1 | -.036 | -.164* | .028 |
| | Sig. (2-tailed) | .689 | .274 | .231 | | .662 | .045 | .737 |
| | N | 149 | 149 | 149 | 149 | 149 | 149 | 149 |
| Gender | Pearson Correlation | -.014 | .066 | .089 | -.036 | 1 | -.075 | .049 |
| | Sig. (2-tailed) | .869 | .425 | .280 | .662 | | .365 | .551 |
| | N | 149 | 149 | 149 | 149 | 149 | 149 | 149 |
| Age | Pearson Correlation | -.425** | .230** | -.057 | -.164* | -.075 | 1 | .076 |
| | Sig. (2-tailed) | .000 | .005 | .487 | .045 | .365 | | .359 |
| | N | 149 | 149 | 149 | 149 | 149 | 149 | 149 |
| HbA1c | Pearson Correlation | -.439** | -.049 | -.056 | .028 | .049 | .076 | 1 |
| | Sig. (2-tailed) | .000 | .549 | .497 | .737 | .551 | .359 | |
| | N | 149 | 149 | 149 | 149 | 149 | 149 | 149 |

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

[11]. Most evidence points to the vitamin D receptors (VDRS) gene in both types of diabetes. VDR as a potential gene for type 2 diabetes (T2D) susceptibility [11,12]. It has been proven that low vitamin D is associated with T2D, which attributed this to two main causes; first, vitamin D stimulates insulin secretion by pancreatic b cells; thus, vitamin D deficiency is associated with insulin resistance. Vitamin D deficiency causes inflammation and increases inflammatory markers. Moreover, it's associated with metabolic syndrome development and genetic polymorphism of vitamin D may lead to impaired glycemic control [13]. On the other hand, other authors concluded that, although there was a significant inverse observational connection between vitamin D and type 2 Diabetes, revealed a lack of support for a causal relationship [14]. While there has been research suggesting that vitamin D may play an important role in glucose homeostasis, the results are conflicting. Many studies have found that insufficient vitamin D status was associated with the development of type 2 diabetes, diabetic complications, obesity, and metabolic syndrome [15]. No significant associations between concentrations of vitamin D and HbA1c were detected. Vitamin D has been hypothesized to exhibit anti-diabetic properties by regulating insulin secretion or insulin sensitivity, producing anti-inflammatory effects, and down-regulation of elevated parathyroid hormone levels, which impair insulin secretion [15].

The role of vitamin D in type 2 diabetes is suggested by a seasonal variation in glycemic control reported in patients with type 2 diabetes being worse in the winter, which may be due to prevalent hypovitaminosis D as a result of reduced sunlight in winter.

According to these results there is a strong significant correlation between Vitamin D levels and HbA1c levels. Patients with well-controlled diabetes (HbA1c <7%) had higher Vitamin D levels. Patients with poor glycemic control (HbA1c >10%) had lower Vitamin D levels. This suggests that Vitamin D deficiency might be linked to poor diabetes control. Considering Chi-Square Value = 20.670, p-value = 0.024, there is a significant correlation between diabetes duration and Vitamin D levels ($p < 0.05$). We analyzed the correlation between Vitamin D and HbA1c and compare Vitamin D levels across different HbA1c groups. It resulted correlation Coefficient (r) = -0.439. This suggests a moderate negative correlation between Vitamin D levels and HbA1c. Higher Vitamin D levels are associated with lower HbA1c values.

Although the function of vitamin D in regulating blood glucose is still not fully understood, vitamin D status appears to play a role in the onset and management of diabetes mellitus. Most studies conducted to discuss the effects of vitamin D on glucose metabolism supported the hypothesis that appropriate vitamin D supplementation may improve the metabolic regulation of glucose levels in type 1 diabetes; in contrast, most of the studies showed no significant improvement in the levels of hemoglobin A1C in type 2 diabetes with supplementation of vitamin D. As the prevalence of diabetes rises and vitamin D insufficiency is quite common, more investigations and research are required to figure out the exact link between vitamin D and diabetes [11].

Severe Vitamin D deficiency (<10 ng/ml) is more common in older age groups (>65 years). Younger groups have slightly better

Vitamin D levels. There is no significant correlation between age and HbA1c ($p > 0.05$). Glycemic control varies across different age groups, but no clear trend is seen. There is no significant correlation between Vitamin D levels and gender, coffee consumption, sweetener use and place of residence.

## Conclusions

Higher Vitamin D levels are linked to better glycemic control (lower HbA1c). Vitamin D levels do not strongly correlate with diabetes duration, though a slight decline is observed in long-term diabetics. Vitamin D levels tend to decline with age, which could contribute to worsening glycemic control in older diabetics, but the correlation is weak. Younger diabetics generally have higher Vitamin D levels compared to older ones.

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